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*Special Supplement:*
*NIH Portfolio on the Automated*
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## Research Advances

In Animal Studies...

# TOLEDO COUPLE FINDS ACUPUNCTURE MAY WORK THRU AUTONOMIC NERVOUS SYSTEM

A husband and wife research team has uncovered preliminary evidence in animals that acupuncture works through the body's autonomic nervous system, thereby providing an explanation for the ancient Chinese procedure which disputes contentions that its effects are psychosomatic or hypnotic.

Do Chil Lee, M.D., assistant professor of anesthesia at the Medical College of Ohio, Toledo, and his wife, Myung O. Lee, M.D., research associate, have induced instrument-measurable, cardiovascular effects on anesthetized dogs with acupuncture, and then blocked these effects with a drug whose action is specific in interfering with a division of the autonomic nervous system. Their work is supported by a General Research Support Grant from the NIH Division of Research Resources.

The Lees' experiments on animals anesthetized with halothane have tested the validity of contentions that acupuncture works primarily through hypnosis or psychosomatic effects. Unconscious animals presumably would be immune to such effects.

The Lees first noticed that acupuncture corrected minor, naturally-occurring cardiovascular abnormalities such as sinus arrhythmia and pulsus alternans in sleeping dogs.

Sinus arrhythmia is a fairly common condition in which the heartbeat alternately increases and decreases, the increase usually occurring when the patient inhales and the decrease when he exhales. It is not considered a sign of disease, and treatment is seldom necessary.

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Pulsus alternans is a condition in which the pulse produced by contraction of the heart varies from strong to weak. This is usually thought to be due to an insufficiency in the function of the heart's ventricles.

Correction of these abnormalities led the Lees to suspect that the effect of acupuncture was mediated through the autonomic nervous system since atropin, a drug known to produce parasympathetic activity associated with the autonomic nervous system, produces like results.

Similarly the effects of epinephrine, also known as adrenalin, in reversing cardiac arrest and increasing cardiac output were duplicated by the Lees using acupuncture. Epinephrine stimulates the sympathetic division of the autonomic nervous system.

According to the Lees, on the one hand, acupuncture appeared to produce an atropin-like or parasympathetic effect while, on the other hand, it produced an epinephrine-like or sympathetic effect. Both effects apparently involved the autonomic nervous system which controls many of the body's involuntary functions, including arterial blood pressure, heart rate, movement of the digestive tract, secretion of digestive glands, and dilation of the pupils of the eyes.

There are two separate divisions of the autonomic nervous system, the sympathetic and the parasympathetic. The effect of the two divisions on the organs generally is antagonistic.

If, for example, the sympathetic division increases activity of a muscle, dilates a blood vessel, or stimulates other activity, the parasympathetic division will act in the opposite manner: it will decrease muscle activity, constrict the blood vessel, or inhibit activity.

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The Lees then attempted to again use acupuncture to increase cardiac output. But this time, the sleeping animals were under the influence of the drug propranolol. Known as a beta blocking agent, it specifically blocks the action of certain of the chemicals secreted by the sympathetic nervous system.

In fact, propranolol blocked the expected cardiovascular effects of acupuncture. The Lees concluded that acupuncture under these circumstances probably results in stimulation of certain elements of the sympathetic nervous system.

The acupuncture point the Lees used to increase cardiac output is known as Jen-Chung or GO-26 and is located in humans at the philtrum or medium vertical groove of the upper lip.

Cardiac arrest was reversed at an acupuncture point known as Jen Ying or ST-9 located in the neck near the side of the larynx. Normal heart rhythm and pulse were restored at a point located at the interior side of the wrist joint in humans, known as Ynag-Hsi or LI-5.

The Lees presented their findings at the Third World Symposium on Acupuncture which was held in March 1975 in New York, NY. Earlier they published a monograph in the January 1975 issue of the *Journal of Surgical Research*.

*The photographs on the following page show Do Chil Lee, M.D., and his wife Myung O. Lee, M.D., at work in their Medical College of Ohio laboratories. (NIH Photos #1378, 1379, 1380)*

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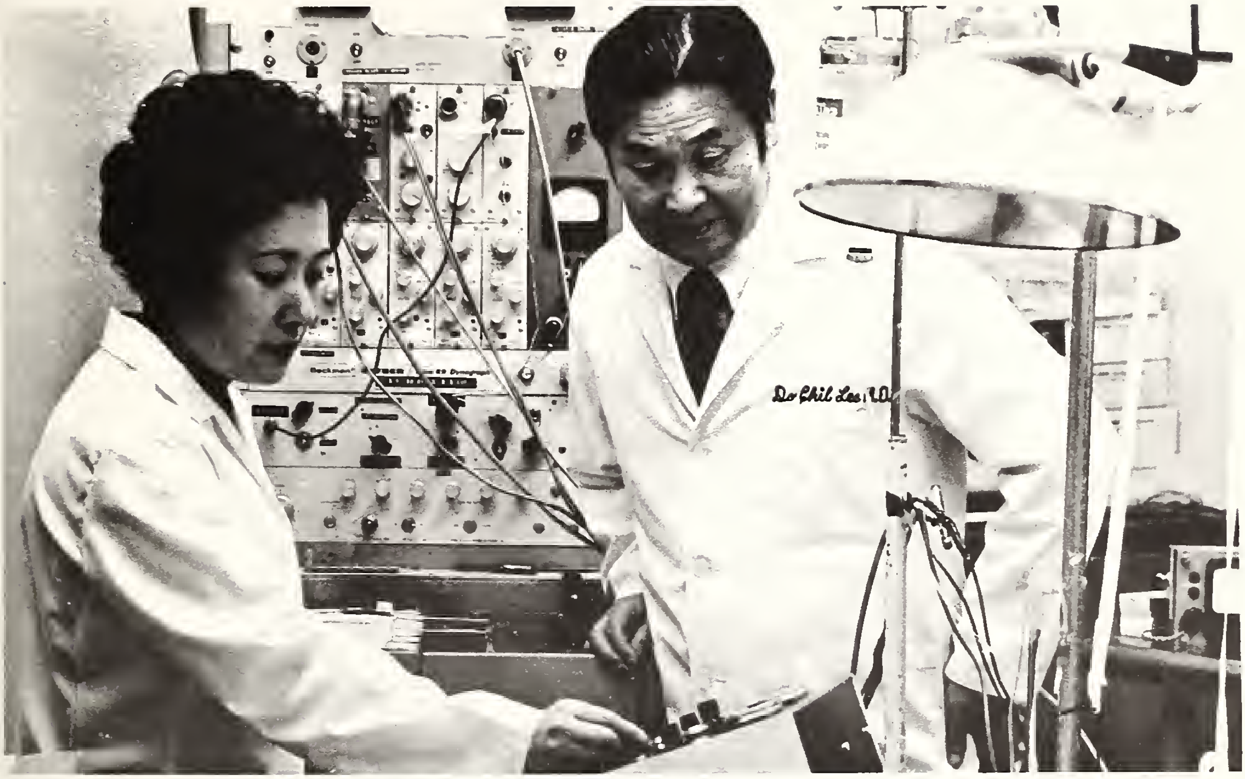
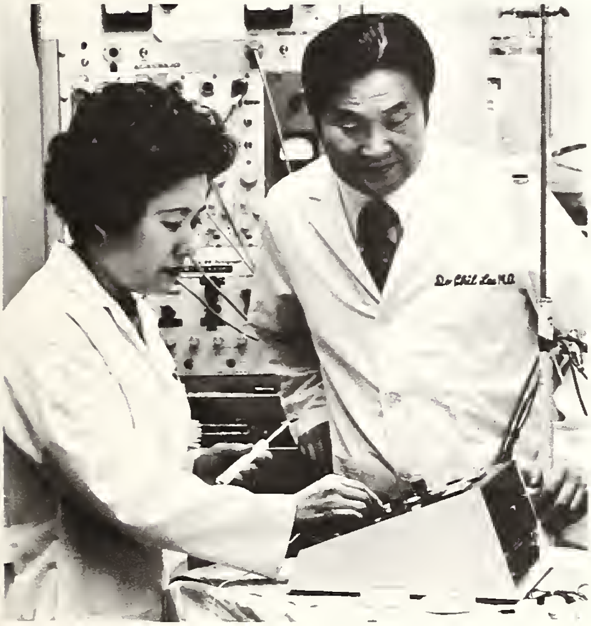
## Acupuncture (Cont'd)


Do Chil Lee, M.D.


Do Chil Lee, M.D.

*(See caption on page 3.)*

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## Research Advances

In Animal Studies...

### ROLE SEEN OF GLUCAGON IN HYPERGLYCEMIA OF DIABETES

Dallas scientists have obtained evidence in animal studies to indicate that development of diabetic hyperglycemia requires the presence of glucagon as well as lack of insulin. Glucagon suppression might help control elevated blood glucose levels in diabetes.

Recent research has suggested that diabetic hyperglycemia may result from a lack of insulin coupled with an excess of glucagon, rather than from insulin deficiency alone. For example, relative glucagon excess is found in both spontaneous and experimental diabetes, including that produced by pancreatectomy. Moreover, in such settings, a simultaneous suppression of both hormones produced by somatostatin administration does not result in hyperglycemia.

The present study has shown that glucagon suppression by somatostatin either reduces or abolishes hyperglycemia in insulin-deficient dogs. This finding supports the hypothesis that development of severe diabetic hyperglycemia requires the presence of glucagon, whether secreted by pancreatic alpha cells or by newly identified gastrointestinal alpha cells, as well as lack of insulin. It also suggests that glucagon suppression might help to improve therapeutic regulation of blood glucose levels in diabetes.

In normal dogs, when both insulin and glucagon were suppressed to unmeasurable levels by somatostatin, hyperglycemia occurred only when exogenous glucagon was infused and was reduced when the infusions were discontinued. In insulin-treated, alloxan-diabetic dogs, continuous somatostatin

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infusion profoundly suppressed plasma glucagon levels and simultaneously abolished hyperglycemia, an effect which persisted even when insulin therapy was discontinued.

When arginine, a potent stimulus of glucagon secretion, was infused in pancreatectomized dogs, plasma glucagon more than doubled, indicating the presence of glucagon-secreting cells in tissues other than the pancreas. The source of this extrapancreatic glucagon was traced to the canine gastric fundus, where a second type of alpha-like cells were found with secretory granules indistinguishable from pancreatic alpha cells.

These findings challenge several long-accepted concepts of diabetes. Excess glucagon, rather than mere insulin lack, may be important, if not essential, for development of the full hyperglycemic syndrome; and conceivably, overproduction of glucose (observed in all forms of diabetes) could be secondary to relative hyperglucagonemia derived from pancreatic and/or gastrointestinal alpha-cells. Moreover, insulin suppression of glucagon, rather than direct insulin action upon the liver, could be the mechanism that decreases hepatic glucose production. Finally, an induced glucagon blockade might achieve and sustain normal blood glucose levels in diabetics, a goal not attained by present methods of treatment.

Roger H. Unger, M.D., of the University of Texas Southwestern Medical School, Dallas, and associates reported their study in *Science*, February 14, 1975. His work is supported in part by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

#

Research Advances

## VITAMIN D METABOLITE USED IN BONE PROBLEM

Patients with uremic osteodystrophy (defective bone formation) have responded to small quantities of the vitamin D metabolite, 1,25-DHCC, with beneficial changes in certain indices of altered calcium homeostasis and in skeletal pathologic findings, report some Minnesota investigators.

Vitamin D is converted in the liver to 25-hydroxy vitamin $D_3$ and then by the kidney to its most active form, 1,25-dihydroxy vitamin $D_3$ (1,25-DHCC). Short-term oral administration of 1,25-DHCC to patients with advanced renal failure improves calcium and phosphorus balance, enhances intestinal calcium absorption, and corrects or improves hypocalcemia. Its effects on the skeletal lesions of uremic osteodystrophy, however, had not been known previously.

The present study describes the effects of 1,25-DHCC on skeletal abnormalities and parathyroid function in patients with advanced renal failure. Administration of small quantities of the hormone markedly reversed hyperparathyroid manifestations and improved the lesions of osteomalacia, and it is believed that further therapeutic trials of 1,25-DHCC are warranted in patients with uremic osteodystrophy.

Skeletal abnormalities and plasma immunoreactive parathyroid hormone (iPTH) levels were evaluated in eight patients with uremic osteodystrophy who were treated with 0.14 to 0.68 micrograms per day of 1,25-DHCC for eight to 17 weeks. Anterior iliac crest bone biopsies were obtained for morphological evaluation before and after treatment, and blood samples were drawn serially for measurement of calcium, phosphorus, alkaline phosphatase, and

(more)

Vitamin D (Cont'd)

iPTH before and during treatment.

Serum calcium levels increased in all patients, while serum phosphorus changes were small and variable, and plasma iPTH levels decreased noticeably in six patients. Bone biopsies showed a reduction in resorptive surface in four patients with osteomalacic lesions, osteoid width was reduced slightly in three and calcification front improved in two.

Although calcium and aluminum hydroxide gel can partially suppress the secondary hyperparathyroidism of renal failure, the characteristic skeletal abnormalities often persist. Thus, 1,25-DHCC therapy may be more efficacious, and studies of more prolonged treatment of such abnormalities may have implications concerning both their pathogenesis and most appropriate therapy.

Anthony Norman, M.D., David Baylink, M.D., and Jenifer Jowsey, M.D., of the Mayo Foundation, Rochester, Minnesota, and associates reported their findings in the *Archives of Internal Medicine,* January 1975. The research is supported in part by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

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LARGEST LIBRARY--The world's largest library in a single scientific field is the National Institutes of Health's National Library of Medicine. The Library houses nearly 1.5 million books, journals, and other materials.

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TOOTH DECAY--Only two percent of Americans escape tooth decay for a lifetime, according to the National Institutes of Health. Also, American mouths probably contain one billion unfilled cavities at any time.

#

## SPECIFIC DIET APPEARS TO AFFECT PREGNANCY IN MONKEYS

The ability of female monkeys to achieve and maintain a pregnancy is greatly reduced after six months on a diet containing polychlorinated biphenyls (PCB's) at the same or lower levels than allowed in some human food.

This finding resulted from a study by Deborah Barsotti and James Allen, M.D., at the Wisconsin Regional Primate Research Center, supported by the NIH Division of Research Resources. It was reported at the April 1975 annual meeting of the Federation of American Societies for Experimental Biology.

Ms. Barsotti and Dr. Allen gave one group of eight adult female rhesus monkeys a diet containing PCB's at half the level (2.5 parts per million) deemed safe in some food products. (The Food and Drug Administration currently considers certain foods--such as fish and poultry--with less than five parts per million of PCB as safe for humans.) After six months on the diet, only three of these eight females became pregnant following three matings with normal, untreated male monkeys. In another group of eight females receiving PCB's at levels accepted for certain foods (5 parts per million), only one was impregnated. In a similar group of untreated females, on the other hand, nine out of 10 conceived after three matings with normal males.

The effect of PCB's on male reproductive capability was not so drastic, the Wisconsin researchers noted. In fact, male rhesus monkeys receiving the higher PCB dose of five parts per million continued to father offspring by normal females at the usual rate after one year of exposure.

Female rhesus monkeys have a 27-day menstrual cycle and are similar to human females in many other regards. Consequently, they are ideally suited

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as "models" for human females in studies on reproduction.

In this study, the PCB diet lengthened the period of menstrual flow and increased menstrual bleeding. Exposure to PCB's also increased the metabolism of steroid hormones in the female monkeys, and these altered hormone levels may have been responsible for the reduced rate of successful pregnancies, Dr. Allen explained.

Previous studies by Dr. Allen's research unit had shown that monkeys display pathological symptoms such as hair loss, acne, and enlarged livers when fed diets with high levels (25 to 300 parts per million) of PCB's. The present work is the first indication that levels of PCB's permissible in certain human foods have profound consequences when consumed by nonhuman primates.

It is not known whether prolonged daily intake of PCB's at low levels would have similar upsetting effects on human reproduction.

PCB's are extremely stable chemicals that have been used in industry for the last 40 years. During this time they have entered the environment, have accumulated because of their long life, and have become contaminants. PCB's, which are stored in body fat, are found in many food items and have been detected in 30 percent of randomly sampled inhabitants of the United States.

This research was financed by the UW-Madison Sea Grant College Program and was conducted at the Wisconsin Regional Primate Research Center and the Biotron on the University of Wisconsin-Madison Campus. The Wisconsin Primate Center is one of seven such NIH-supported research facilities conducting biomedical research on primates aimed at human health needs.

#

Research Advances

Dental Research...

## IMMUNOLOGISTS STUDY TISSUE DESTRUCTION

National Institute of Dental Research (NIDR) immunologists have reported that bacterial products (endotoxins) can stimulate both T and B lymphocytes to divide and release active substances that attract wandering cells (macrophages) and induce them to release an enzyme which destroys tissues that support teeth.

The scientists first noticed that wandering macrophages congregate in severely inflamed gingival (gum) tissues. When these cells were cultured with bacterial endotoxin, they would enlarge, divide, and release the enzyme collagenase. This enzyme cleaves the collagen molecule into shorter pieces which are susceptible to digestion by other enzymes. Collagen is the major protein component of connective tissue and, as it breaks down, the connective tissue framework of the gums is destroyed.

Bacterial endotoxins also stimulate lymphocytes to divide and release active substances called lymphokines into the culture fluid. One lymphokine attracts the macrophages and another lymphokine can stimulate the macrophages to produce collagenase.

Immunologists can now distinguish two kinds of lymphocytes, B cells derived from bone marrow and T cells which come from the thymus gland. These lymphocytes look alike but usually behave differently in the body's immune system. B cells interact chiefly with the humoral immune system which involves substances such as antibodies, antigens, and serum complement enzymes in the blood. T cells play a large role in the cellular immune system by

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responding to antigens and triggering reactions in other cells such as macrophages.

Endotoxin comes from cell walls of certain bacteria. It contains complex sugars bound to a lipid. The scientists found that only the lipid fraction triggered reactions in B lymphocytes while the sugar portion stimulated sensitized T lymphocytes. NIDR research indicates that both T and B lymphocytes can be stimulated to divide by other substances including mitogens and specific antigens. Thereafter, both release lymphokines. One type of lymphokine attracts macrophages, another prevents them from wandering further, and a third stimulates them to make enzymes including collagenase.

Dental plaque--consisting of bacteria, their products, and salivary substances--is in contact with the mucosal lining of the mouth and hence with the immune system. The chronic stimulation of the immune system could account for the high concentrations of collagenase found in the diseased gingivae. Collagenase is thought to attack the collagen in gum tissue leading to gingivitis and bone destruction.

Parts of this research were reported in the *Proceedings of the National Academy of Sciences* in September 1974; at the Eighth Miles International Symposium Series in August 1974; and in *Science*, January 24, 1975. Larry M. Wahl, Ph.D., Sharon M. Wahl, Ph.D., Stephan E. Mergenhagen, Ph.D., and George R. Martin, Ph.D., collaborated in the work.

#

New Syndrome...

## GENETIC DISORDER AFFECTS TOOTH ENAMEL, FINGERNAILS

University of Minnesota scientists have reported finding a new genetic syndrome in which many teeth do not erupt but resorb in the jaw, and the soft brown enamel of those that do erupt is poorly developed. Fingernails tend to be dark and detached. Also, many oily dermatologic lesions develop on the scalp from too much sebum, although the hair appears to be normal. Finally, the skin is very dry and rough because functional sweat glands are few. These individuals have abnormal fluctuating body temperatures and prefer cold weather.

The investigators, whose work is funded by the National Institute of Dental Research, reviewed 37 known syndromes with defective ectodermal development and found that none of those clusters of hair, teeth, nail, and skin problems matched the particular problems of ten members who span three generations of this Caucasian family of Scandinavian descent.

The dominantly-inherited condition is not sex-linked, and affects both males and females. It is not associated with mental retardation, deafness, or unusual hair characteristics as are many ectodermal dysplasias.

The study was reported in *Oral Surgery, Oral Medicine, Oral Pathology,* January 1975, by Carl J. Witkop, Jr., D.D.S., Louise J. Brearley, M.D.Sc., and William C. Gentry, Jr., M.D.

#

News Feature

## ASPIRIN SUBSTITUTE MORE EFFECTIVE THAN NARCOTIC IS FOR DENTAL PAIN

Acetaminophen (Tylenol), the most common aspirin substitute, is more effective than the usually prescribed dose of codeine for relief of moderate to severe pain following dental surgery, a Georgetown University study reveals.

The finding is from the second in a series of Georgetown studies evaluating the effects of mild pain killers on dental patients. The first study, which compared aspirin and codeine, showed similar results.

Results of the two studies were presented at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics in March, 1975.

Georgetown researchers chose acetaminophen for the study because it is the major aspirin substitute for many people, and has fewer known side effects than aspirin. Unlike aspirin, acetaminophen neither causes possible gastric irritation (a problem for the ulcer patient) nor does it interfere with the blood clotting process (an important consideration for oral surgery patients who are prone to bleeding problems).

"Our studies have shown two leading over-the-counter pain killers (aspirin and acetaminophen) are more effective in postoperative dental pain than the most commonly used narcotic," said Stephen A. Cooper, D.M.D., a Georgetown researcher.

"This is most important to the consumer. Not only are these drugs less expensive, but they allow the patient to function better with fewer side effects."

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Dental surgery causes an inflammatory reaction with pain and swelling, Dr. Cooper explained. A locally acting antiinflammatory drug may be more important than a centrally-acting narcotic for this type of pain. Recent evidence shows that acetaminophen and aspirin have antiinflammatory properties.

"Perhaps the future of treating dental pain may be in the direction of finding more effective antiinflammatory agents, rather than turning to potent narcotics which carry more dangerous side effects," Dr. Cooper suggested.

The Georgetown study involved 160 healthy patients whose impacted wisdom teeth, imbedded under bone and tissue, were removed at the GU Oral Surgery Clinic. The participants, who ranged in age from 16 to 35, were given local anesthesia and required sutures after surgery.

The patients returned home after surgery, and needed effective pain relief that would not interfere with their ability to function.

Each patient was randomly assigned a single dose of either placebo, codeine (60 mg.), acetaminophen (600 mg.), or a combination of acetaminophen and codeine. Researchers instructed patients to take the medication when they suffered moderate to severe pain. Within several hours after surgery, 98 percent of the participants needed help for pain.

Each hour for a three-hour period following medication, the patients recorded the intensity of pain, the amount of relief provided by the treatment, and any side effects.

Analysis of this data showed that acetaminophen was significantly more effective than codeine for pain relief. The acetaminophen-codeine combination was not significantly superior to acetaminophen, but was better than placebo.

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The codeine treatment was not significantly better than placebo, although codeine's side effects of drowsiness and nausea may have contributed to this result. Codeine alone and in combination with acetaminophen produced more side effects than the other treatments.

William Beaver, M.D., of Georgetown University collaborated with Dr. Cooper in the study, which was supported by the National Institute of Dental Research.

#

PSORIASIS--Nearly eight million Americans have the reddish patches of skin called psoriasis. Psoriasis is hereditary and only one parent need be affected for a child to develop psoriasis, according to the National Institutes of Health.

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RETINAL DETACHMENT--Retinal detachment is a separation of the inner from the outer layer of the retina, the light-sensitive tissue at the back of the eye. The National Institutes of Health reports that this condition, which can cause permanently impaired vision, occurs most commonly in men, the very nearsighted, and the aged.

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METABOLISM--Metabolism is the amazing process whereby the body biochemically transforms food into tissue elements and into energy for growth, repair, and general body functions, according to the National Institutes of Health.

#

Photo Feature

In Animals...

## MILK-BORNE WHITE CELLS CAN CAUSE GRAFT-VS.-HOST DISEASE

Although mother's milk may provide an infant with "ready-made" protective antibodies, National Institute of Allergy and Infectious Diseases grantees have now shown, in animals, that milk-borne immunologically-competent cells may, under certain conditions, produce graft-versus-host disease.

Nature has provided mechanisms to protect the newborn infant in its hostile new environment until its own immunologic system develops. In certain species including man, the fetus is passively immunized by maternal antibodies which cross the placenta. After birth, the infant receives, via mother's milk, antibodies which are believed to protect it against certain organisms, particularly those infecting the intestines. Although mother's milk also contains white cells, their function is still unknown.

To determine whether these milk-borne white cells are immunologically competent, Texas scientists studied the effects of milk on rats nursed by natural and/or genetically different foster mothers. Alterations in the immune responses of the infant rats were defined by their rate of rejection of skin grafts from rats of the same strain as the foster mothers.

A group of Fischer (FI) rats--nursed by foster Lewis (LE) mothers--rejected their LE grafts at a slower rate than did FI rats nursed by their own mothers. This slower rate of rejection indicates that the infants did receive sufficient LE cells to induce a feeble degree of tolerance to the LE skin grafts.

(more)

Cells (Cont'd)

However, 31 percent of these foster-nursed rats developed graft-versus-host disease (GVH) and died. GVH occurs when a graft of genetically non-identical but immunologically competent cells rejects the recipient who, for various reasons, is incapable of mounting an immune response against the graft. According to the researchers, the development of GVH further proves that the immunologically naive infant rats must have received immunologically mature and incompatible LE cells in the foster mother's milk.

The absence of GVH in a group of FI rats who were nursed by their own mothers for 24 hours before being transferred to foster LE mothers may be significant. The researchers believe that these infants probably received, in that short time, a sufficient quota of their own mother's immunologically competent and compatible cells which enabled them to destroy or inactivate the potentially harmful LE cells which they subsequently received from the foster mothers. When LE cells were encountered a second time via the skin graft, the adult FI cells--"primed" by their initial contact with the milk-borne LE antigens--helped these infants to reject the grafts at a faster rate than the rats nursed solely by their own FI mothers.

These experiments have revealed a completely-unrecognized and potentially-important example of the natural transplantation of cells. Although certain immunologic protective benefits are conferred on the infant rat by these milk-borne cells, they may also be a potential cause of unwanted or harmful immunologic responses. It is not yet known whether a similar process occurs in humans, although human breast milk does contain high concentrations of viable cells derived from the bloodstream.

(more)

Cells (Cont'd)

*Rupert Billingham, M.D. (left), Alan Beer, M.D., and Judith Head, M.D., of the University of Texas Southwestern Medical School at Dallas conducted NIH-funded research which showed that milk-borne immunologically-competent cells may produce graft-versus-host disease. (NIH Photo #1381)*

#

NORMAL VOLUNTEERS--By studying healthy volunteers at the National Institutes of Health Clinical Center, scientists gain insights into body functions in disease. The normal volunteers are often from church groups, civic organizations, and student groups.

#

News Feature

Strong Gel vs. Weak Rinse...

## INVESTIGATORS TEST FLUORIDE ON SCHOOL CHILDREN'S TEETH

Scientists at the Forsyth Dental Center, Boston, are beginning a study of 900 nearby school children to learn whether a ten-day series of daily applications of a strong fluoride gel will protect teeth from decay better than daily mouth rinsing with a weak fluoride solution.

Paul F. DePaola, D.D.S., and Pramod Sopakar, D.D.S., whose work is supported by the National Institute of Dental Research's National Caries Program, also hope to detect whether or not these two treatments in conjunction interact to improve protection. No one has yet demonstrated the interaction of fluoride treatments although some methods seem to have an additive effect. It is thought that fluoride may work in two different ways. Applications of strong fluoride apparently make the tooth's enamel surface more resistant to bacterial acids when the fluoride is incorporated into or bound on the surface of the enamel crystals. Treatments with fluoride solutions so dilute that they do not appreciably raise the level of fluoride in teeth presumably work by interfering with the ability of mouth bacteria to ferment foodstuffs.

The school children live in Somerville, an area where natural fluoride in the local water supply is only 0.4 parts per million. Few of these children see a dentist regularly, and their rate of tooth decay is high. Annual school surveys show only 10 percent of Somerville's school children require no dental treatment, while 75 percent have teeth that need repair, and 15 percent should have some extractions. These youngsters develop about three new cavities each year.

(more)

Fluoride (Cont'd)

After a professional tooth examination, all parents will be notified of their children's needs, and, upon request, diagnostic X-ray films will be sent to their dentists. However, the research will take very little school time.

The scientists plan to accept the first 900 children of the 12-year-olds who apply. The two dentists will examine their teeth annually, treat them for two years, and, at the end of the third year, make a final tooth survey.

The youngsters will be randomly assigned to one of four groups. During ten consecutive days for five minutes a day, the first group will bite into individually fitted mouth pieces filled with a 1.23 percent fluoride gel. Thereafter, they will rinse their mouths daily for one minute with a 0.023 percent fluoride solution. The following year the rinses continue. Although there will be no treatment in the third year, a final examination at its end will show how much protection has been given.

The other groups of children will follow the same procedure, but there will be no fluoride in the gel of the second group. The third group will have fluoride in their gel but none in their mouth rinse. The fourth group will have no fluoride in either gel or rinse; so they will serve as controls for the experiment. One dentist will examine the same children throughout the three year span, and X-ray radiographs will also be taken at each examination to detect and record any hidden decay.

Dental hygienists will oversee the treatments and record attendance, while assistants will prepare for and clean up after the treatments which will be done on a regular schedule in fairly large groups in the school cafeterias.

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Three junior high schools located close together are cooperating in the venture. Findings will be analyzed statistically with help from John Alman of the Boston University Computing Center.

#

DATA CENTER--A National Microbial Data Center is being developed at the American Type Culture Collection in Rockville, Maryland, according to Micah I. Krichevsky, Ph.D., of the National Institute of Dental Research (NIDR).

Dr. Krichevsky said the new center would be available to assist dental researchers throughout the world. In addition to NIDR, Dr. Krichevsky said the center would be supported by the Food and Drug Administration and under grants to the University of Maryland.

The American Type Culture Collection is the repository of the largest number of type species of bacteria in the world. In consultation with project director, Rita R. Colwell, Ph.D., professor of Microbiology, of the University of Maryland, Dr. Krichevsky's staff is collaborating in establishing a computerized data bank into which will be deposited many kinds of information about bacteria. Scientists at the Center for Disease Control, Atlanta, the Forsyth Dental Center, Boston, the University of Pennsylvania's Dental School, Philadelphia, and the University of Miami's Institute of Oral Biology, and others have already supplied much information.

These data will be systematized and arranged so that scientists may retrieve answers to a variety of questions. Dr. Krichevsky hopes that through this data bank the special characteristics and biological principles which control many organisms, and especially those which affect oral health, will become evident.

#

News Feature

## RESEARCHERS DISCOVER RARE CLOTTING FACTOR

Doctors at the University Hospitals of Cleveland have discovered and isolated a rare clotting factor missing in the blood of certain individuals. They hope this discovery will lead to better understanding of clotting and inflammation mechanisms in the body.

While the blood of a normal person clots in a test tube in approximately ten minutes, blood from one of their patients takes an hour or longer to clot. This patient does not bleed abnormally and apparently is protected by an unknown alternate clotting mechanism.

Apart from helping to yield an eventual explanation of the clotting mechanism, this factor has been found to play a role in the inflammatory response which is present in many disease processes.

Hidehiko Saito, M.D., assistant physician in the department of medicine at the Case Western Reserve University School of Medicine, and Oscar D. Ratnoff, M.D., co-director of the division of hematology, confirmed that the abnormally-slow clotting time of the patient's blood must be due to some unknown factor which was absent. This they called the Fitzgerald factor, after the patient. Since that time, three similar cases have been reported in other cities. In 1955 Dr. Ratnoff identified and named the Hageman factor, another clotting factor.

When blood is exposed to or has contact with a foreign surface, such as skin, metal, or glass, two processes result, blood clotting and a reaction called kinin generation. Kinin is a protein which, though it is

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very small, has a strong biological action. It induces pain, inflammation, swelling, contraction of smooth muscles, and decreased blood pressure. Both the Hageman and Fitzgerald factors are necessary for clotting and kinin reactions.

Dr. Saito indicates that, according to the studies of blood in the test tube, certain patients should have trouble with both clotting and kinin generation; they actually have none. "There's an auxiliary device which we don't understand," he said. "There must be an alternate mechanism which prevents the patient's bleeding profusely whenever he is injured."

There is a great discrepancy between what happens in the test tube and what happens in the bodies of these patients, but the mechanism which seems to operate clotting is still unknown.

The investigators plan to continue their research, supported by the National Heart and Lung Institute, on the Fitzgerald factor, now that they have succeeded in isolating it from normal plasma.

#

MONKEY ATHEROSCLEROSIS--Atherosclerosis can be reversed in monkeys. National Heart and Lung Institute grantees at the University of Chicago report that a low-fat, low-cholesterol diet exerts a positive effect on the reversal of advanced experimental atherosclerosis in Rhesus monkeys. Additionally, the diet decreases the frequency and severity of the fatty deposits in the artery walls. Since monkeys are commonly used as substitutes for humans in atherosclerosis research, the Chicago investigators suggest that these findings might apply to humans.

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News Feature

Diagnosing, Monitoring Disease...

## NIH'S CLINICAL PATHOLOGISTS PERFORM 200 DIFFERENT TESTS

Medical laboratory tests have become essential to measure human health. By analyzing and measuring the constituents of body fluids and wastes physicians can diagnose and monitor the progress of disease. They can detect and identify the cause of infection, trace metabolic disorders, watch blood diseases, and determine pregnancy.

At the NIH Clinical Center more than 200 different blood, chemical, and microbiological tests are offered by the Clinical Pathology Department, more than twice the number usually needed in general hospitals the same size. The greater number and variety of tests are used because most Clinical Center patients have diseases that physicians, as yet, do not know enough about. The tests are requested in hope of gaining a clue to the disease process. As many as 25 to 30 tests may be performed on each fluid sample, for example, and many are repeated each day. In total, over 1.1 million laboratory tests were performed in the hospital last year.

To meet this unusual demand for laboratory services, the department has pioneered in design and use of precision instruments that now perform 80 percent of the tests automatically. For example, the SGOT test for enzymes in the blood (used to determine the nature of acute heart attacks) has been automated. Previously, a technician had to repeat the test four times, measuring with a stop watch the time it took for certain reactions to occur. Now, an instrument withdraws an appropriate amount from the sample, adds chemicals, incubates the mixture, and reads and calculates the enzyme activity

(more)

Tests (Cont'd)

faster and more accurately than was previously possible by hand. The equipment is connected to a computer that records the test results and, at designated times each day, combines them with results of other tests on that patient and types a report for use by physicians.

In the Hematology Laboratory blood constituents are identified, counted, and analyzed. By monitoring red blood cells that carry oxygen and nutrients to the body, white cells and other blood elements that fight infection, platelets and related blood substances that aid in clotting, and numerous other blood constituents, physicians can diagnose many diseases and watch the progress of their patients.

Each month 30,000 blood tests are performed in the Hematology Laboratory. This is nearly four times the number required by a general hospital of the same size. Sixty percent are performed by automated equipment. However, many special tests requested for patients with serious blood diseases, such as anemia or leukemia, must be performed by hand. These include special checks to determine which type of infection-fighting white cells are absent or in short supply, or which blood element is responsible for blood that does not clot properly.

For outpatients, blood tests must be performed immediately so their doctors know the answers before the patient leaves the hospital for the day. This work is performed by a staff of technologists, many of whom have academic degrees in biology and related fields. Some are also certified for additional training in laboratory techniques.

In the near future the hospital will install a master computer system

(more)

that will permit results of these and other laboratory tests to be reported immediately to the physicians and nurses waiting in the patient areas of the hospital. The computer will combine this information with other data from the patient's record, to give a comprehensive report on the patient's condition. This will make the information available much sooner that is currently possible, eliminate possible errors that may occur when information is transmitted over the telephone or hand written, and free valuable technical personnel for the work that cannot yet be performed by machine.

*An automated pipette was recently developed by NIH staff members to permit chemical analyses of the small amounts of body fluids available from children. Previously such tests had to be performed by hand because the available automated analyzers required larger samples than are generally available from children. (NIH Photo #1382)*

#

News Feature

## FRICATIVE SPEECH ERRORS ARE STUDIED

University of North Carolina investigators of speech defects report that the ability of children with cleft palates to make correctly the fricative sounds *s*, *z*, *f*, and *v* depends to a considerable extent upon their ability to control the opening at the front of the mouth.

All but a few nasal speech sounds require that speakers close the velopharyngeal gap between the nose and the throat behind the palate since closure forces the airstream to flow through the mouth past the articulating tongue and lips. Therefore, much speech therapy properly concentrates on showing children how to compensate for slightly short or incompetent palates. Severely deficient palates require surgery before speech therapy is effective.

However, William H. Claypoole, D.M.D., Donald W. Warren, D.D.S., Ph.D., and Doris P. Bradley, Ph.D., found that frequently children who use the tongue to compensate for palatal deficiencies find it difficult to use the tongue to simultaneously reduce the opening at the front of the mouth. This reduced anterior opening is needed to compress the air to produce clear fricatives.

The scientists measured the area of dental spacing or opening in front of the premolar teeth when the posterior teeth were in occlusion, and also measured and compared air pressure and flow during connected speech in the mouths of 30 youngsters. Two of these (eight to 18 years of age) were normal, 10 children with cleft palates (nine to 17 years) had adequate closure at the back of the mouth, and 10 (seven to 25 years) had inadequate velopharyngeal closure. The constriction ability of the opening at the front of the mouth was calculated by a formula from the figures for air pressure and flow. In

(more)

each group the size of the calculated opening varied among subjects but was quite constant for any one person.

The front opening produced by normal speakers while pronouncing fricatives ranged from 0.9 to 9.8 square millimeters, that of cleft palate children with adequate closure went from 0.9 to 6.7, while the openings of children with inadequate closure varied from 0.5 to 54.7. Some of this group closed their mouths too much, but six of the 10 did not close them enough.

The scientists found no correlation between any articulation errors and anterior dental open bite or spacing, but noted that fricative errors, especially for the *s* and *z* sounds, were more frequent among those with larger openings. The work is supported in part by the National Institute of Dental Research.

#

SICKLE CELL--Sickle cell trait, the generally harmless condition, occurs about once in every ten American blacks. Sickle cell anemia occurs about once in every 500 American blacks. At present, it is estimated that there are about 50,000 persons in the United States with sickle cell anemia and about two million with sickle cell trait, according to the National Institutes of Health.

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HEMOGLOBIN--The term "sickle cell disease" refers to all inherited blood conditions in which sickle cell hemoglobin is present. Hemoglobin is the red colored substance in red cells that enables blood to carry oxygen from the lungs to all tissues of the body, according to the National Institutes of Health.

#

## News Releases Issued

NRS AWARDS--Final regulations governing National Research Service (NRS) Awards were announced May 2 by HEW Secretary Caspar W. Weinberger. The National Research Service Award Act of 1974 authorizes the Secretary to make awards directly to individuals for biomedical and behavioral research and research training, and to make grants to institutions to enable them to make NRS Awards to individuals for such training. It also consolidates existing research training and fellowship authorities of the National Institutes of Health and of the Alcohol, Drug Abuse, and Mental Health Administration into a single program.

The program provides that: (1) Recipients of traineeships are subject to service, payback, and recovery requirements; (2) NRS Awards may be made only in those subject areas in which a need has been verified; and (3) NRS Awards must be approved by the respective Advisory Councils, may not exceed a period of three years (subject to Secretarial waiver), and may not be used to support residencies.

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VIRUS GENES--Molecular study of virus-caused cancer of experimental animals has shown, for the first time, that a virus gene is needed not only to initiate the cancerous process in previously normal cells, but must be continually present for the cancer cells to continue growing. The research by scientists of the National Institute of Arthritis, Metabolism, and Digestive Diseases provides concrete evidence for the long-held belief that virus genes become incorporated into a normal cell's gene profile. They then direct abnormal reproduction of the gene material called DNA (deoxyribonucleic acid).

(more)

Virus Genes (Cont'd)

The newly-published NIH report pinpoints at a molecular level the region of a virus which actually initiates and maintains a cancerous change.

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VENEREAL DISEASE--A group of scientists led by John M. Knox, M.D., at the Baylor College of Medicine, Houston, will conduct wide-ranging research on sexually-transmitted diseases under a program-project grant awarded by the National Institute of Allergy and Infectious Diseases (NIAID). The $219,297 grant to Baylor will support the first year of a new research effort on gonorrhea, syphilis, group B streptococcal infections, and herpes simplex virus infections of the genital tract. This project is a part of NIAID's special research grants program initiated in 1974 to facilitate multidisciplinary approaches to the varied problems of sexually-transmitted diseases at institutions where investigators have exhibited special expertise. Currently, the NIAID invests nearly $3 million annually in venereal disease research.

Dr. Knox is an internationally-recognized authority in the field of venereal disease. He will coordinate venereal disease research in the departments of medicine, dermatology, microbiology, virology, and epidemiology at Baylor, as well as related efforts of the Houston City Health Department.

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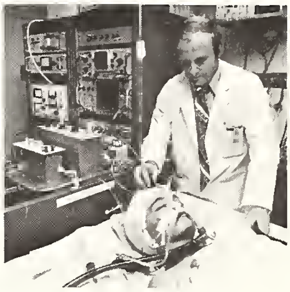

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Research Advances

## ANIMAL MODEL DEVELOPED FOR HERPESVIRUS RESEARCH

Following up on observations made by other scientists, National Institute of Allergy and Infectious Diseases contractors have developed an animal model for human herpesvirus type 2 infection which should permit the evaluation of potential therapeutic drugs and determination of the pathogenesis of the disease.

Infections of the human genital tract with *Herpesvirus hominis* (HVH) type 2 have assumed increasing importance during recent years. Although many infections are without symptoms, local pain can be severe and recurrent disease is common. A significant association of HVH type 2 with carcinoma of the cervix has also been reported.

Genital herpes appears to occur more frequently during pregnancy and can be transmitted to the infant during the birth process. Infection of the newborn with HVH type 2 is serious and has been reported to result in death in more than 70 percent of the cases.

In the present study, investigators at the University of Utah College of Medicine, Salt Lake City, inoculated pregnant and nonpregnant adult female Swiss-Webster mice intravaginally with HVH type 2. The virus preparations were obtained from Andre Nahmias, M.D., Emory University, Atlanta, who reported several years ago that HVH-inoculated female mice developed high virus titers in vaginal secretions and died of encephalitis within 20 days.

The Utah investigators confirmed and extended these findings. More than 90 percent of the pregnant mice in their study developed vaginitis

(more)

Animal Model (Cont'd)

and died, in comparison to 49 percent of the non-pregnant animals. This enhanced susceptibility of the pregnant mouse to genital herpesvirus infection thus parallels the clinical observations made in humans.

At daily intervals the scientists obtained vaginal swabs, blood, liver, spleen, spinal cord, cerebellum brain stem, cerebrum, and olfactory bulb specimens from individual animals and assayed them for the presence of HVH. Virus was never isolated from blood samples or olfactory bulb specimens and rarely from liver or spleen. Herpesvirus was detected in the spinal cord on day 5 but did not appear in the cerebellum brain stem until day 7.

These results indicate HVH type 2 in mice, after initial replication in the mucous membranes of the genital tract, spreads to the spinal cord and then ascends to involve the brain. This experimental infection, therefore, provides a test system not only for drugs which might be effective in localized infections but also for compounds with potential for treating the more serious systemic form of the disease. It should be pointed out, however, that the encephalomyelitis regularly observed in the mice rarely occurs in humans.

This work was reported by Drs. James C. Overall, Jr., Earl R. Kern, Ronald L. Schlitzer, Stanford B. Friedman, and Lowell A. Glasgow in the March 1975 issue of *Infection and Immunity*. All these men are physicians.

#

**NEI PRESS BRIEFING**--The National Eye Institute (NEI) will host its first press briefing on Thursday, June 12, at 10 a.m., as one in the series of NIH Science Writers Seminars. The briefing at NIH will serve as a report on the five-year-old Institute's growth and development, and will provide a forum for discussion of the most significant advances in vision research. For more details, contact Julian M. Morris or Ms. Bonnie F. Spellane at (301) 496-5248.

#

Research Advances

## NEW TECHNIQUE ALLOWS SAFER REMOVAL OF IMBEDDED TUMORS

For the first time the safe removal of deeply imbedded vascular tumors of the brainstem has been made possible by a new technique developed at The New York Hospital-Cornell Medical Center.

The procedure, based on the use of deep hypothermia and circulatory arrest, and its successful application in the first operation of its kind ever to be performed, were described April 7, 1975, by the originator, Russel H. Patterson, Jr., M.D., in a report to the American Association of Neurological Surgeons meeting in Miami Beach.

Dr. Patterson, a pioneer in the development and application of hypothermia and circulatory arrest techniques for intracranial surgery, is attending surgeon-in-charge of Neurosurgery at The New York Hospital-Cornell Medical Center. He is also a professor of Surgery at Cornell University Medical College. Richard A.R. Fraser, M.D., co-author of the report, is an associate professor of Surgery at the Medical College and an associate attending surgeon at The New York Hospital.

In a recent dramatic operation performed under deep hypothermia and circulatory arrest, Dr. Patterson safely removed a large vascular tumor (hemangioblastoma) imbedded in the brainstem of a 42-year-old woman. He had found it impossible to safely remove the tumor in two previous operations in which conventional procedures were used. The danger of hemorrhage, which conventional procedures cannot prevent, imposed too great a risk, since the surgical manipulations that would have been required to control it could damage neural structures.

(more)

Tumors (Cont'd)

The combined use of deep hypothermia and circulatory arrest not only overcome these hazards by preventing hemorrhage but allow the surgeons to work in a dry field for as long as 45 minutes. At normal temperatures the brain is damaged after a few minutes without oxygen supplied by the blood. If the body is sufficiently cooled, however, its functions are halted and the brain tolerates interruption of the blood supply for much longer intervals.

In the case cited by Dr. Patterson, the previous incision in her brain was reopened while her heart and one femoral artery were exposed. After the top of the tumor was exposed, the dura, the tough outer membrane covering the brain, was sewed firmly against the skull to prevent epidural bleeding.

The patient was heparinized to help prevent blood clots. Tubes were inserted in the right atrium and right femoral artery. The patient's circulatory system was hooked up to a heart-lung machine and cardiopulmonary bypass was begun. Her blood was drained, cooled in a special refrigeration unit attached to the machine and re-circulated until her body temperature was sufficiently lowered.

After 25 minutes cardiac action ceased. The esophageal temperature had fallen to 10 degrees C. and the rectal temperature to 20 degrees C. Recirculation of the blood was stopped. Her head was tipped up to enable the blood to drain back into the circuit.

The tumor, now shrunken and deprived of blood, was removed in 19 minutes. Bipolar electrocoagulation was used to coagulate any filmy connection that might inhabit an empty vessel. Bleeding from the tumor bed and craniotomy wound was minor and constituted no problem.

(more)

After the tumor was out, the operating table was leveled. The blood was warmed and re-circulated through her body. Thirty-four minutes later her temperature had risen to normal. Two electric shocks restored her heart to its normal rhythm.

The patient's hearing quickly returned to normal, following the operation. Prior to the removal of the tumor, she was afflicted with bilateral deafness. Her intellectual function, which also had been previously dulled, is normal. During the seven months that have passed since the removal of the tumor, she has shown slow but generally encouraging neurological improvement in other respects. Before the operation her lack of muscular coordination was sufficient to make her bedridden. She can now walk with some help. Although her articulation has improved, she still has considerable difficulty in speaking distinctly.

Before the introduction of his new technique, Dr. Patterson found that tumors with an extensive attachment to the brainstem, such as she had, could not be safely operated on unless the surgeon was willing to settle for its partial removal.

"With radiation therapy, a remission measured in years may follow," Dr. Patterson said. "But when the tumor recurs, as it did in her case, the prognosis is bleak," he emphasized, "unless it can be completely removed before the patient is devastated by irreversible neurological defects."

Dr. Patterson has research support from the National Heart and Lung Institute.

#

## Research Advances

### NCI REPORTS ENCOURAGING UPSWING IN EARLY DETECTION OF CANCERS

An increasing number of cancers of the breast, body of the uterus, rectum, bladder, and prostate are being diagnosed when still localized to the site of origin, a National Cancer Institute (NCI) scientist reported on May 1.

These findings are encouraging, according to Sidney J. Cutler, Sc.D., chief of the NCI Biometry Branch, because they indicate that improved diagnostic techniques--coupled with professional and public education about their availability and use--may improve patients' chances of survival. Cancer therapy is more effective when the cancer is treated at an earlier, more localized stage.

Dr. Cutler spoke at the National Conference on Advances in Cancer Management in Denver. The conference is the second in a series co-sponsored by NCI and the American Cancer Society.

Other authors of the study of hospital records for 11 common cancers were Max H. Myers, Ph.D., and Paulette L. White of the Biometry Branch.

The scientists also found that a higher proportion of white cancer patients are diagnosed when their disease is localized than are black patients. This pattern may occur because the white population uses available screening and diagnostic techniques to a much greater extent than the black population, Dr. Cutler said.

Further analysis of localized disease in relation to the age of the patient revealed that the biologic characteristics of a tumor and its behavior in a patient are complex. Many cancers have spread beyond the site of origin by the time the patient experiences symptoms of disease, the NCI

(more)

scientist noted.

Cancers of the body and cervix (or neck) of the uterus, bladder, and ovary are diagnosed at a localized stage more often in younger than in older patients. For cancers of the stomach, pancreas, lung, and prostate, however, individuals between the ages of 25 and 45 are diagnosed with advanced cancers more often than are older patients. To a lesser degree, the same pattern is evident for cancers of the colon, rectum, and breast.

Cancers with the latter pattern may behave differently in younger patients than in older patients, Dr. Cutler said. The cancers may spread more rapidly in younger patients because of the characteristics of the cancer itself or the susceptibility of the patient.

The risk of developing cancer at young adult ages is generally low, but when it does occur it may have spread beyond the organ of origin. This pattern is evident for cancers of the stomach, pancreas, lung, and prostate. Unfortunately, current screening techniques are impractical for application to young adults. There is thus a need for screening and diagnostic methods that identify younger persons at high risk of developing these cancers, Dr. Cutler concluded.

#

CATARACT SURGERY--Cataract surgery is one of the most successful operations performed today. From 90 to 95 percent of patients undergoing this operation regain useful vision, reports the National Institutes of Health.

#

Research Advances

## FAMILY BACKGROUND COULD REVEAL CANCER PRONENESS

Physicians can monitor some individuals at high risk of cancer by identifying familial constellations of cancer, a National Cancer Institute (NCI) scientist reported on May 1.

Scientists at NCI and other institutions have been able to detect early cancers by studying apparently normal members of families that have a high rate of cancer, according to Joseph F. Fraumeni, Jr., M.D., associate chief of NCI's Epidemiology Branch. In some cancer-prone families, NCI scientists have identified immunologic defects, congenital bone abnormalities, or other childhood disorders that predispose individuals to cancer.

Dr. Fraumeni spoke in Denver at the National Conference on Advances in Cancer Management, co-sponsored by NCI and the American Cancer Society.

Identification of various familial cancer syndromes provides physicians with the opportunity to monitor normal family members more closely for the development of cancer, Dr. Fraumeni said. At the same time, intensive laboratory studies that pinpoint risk to cancer may provide scientists with information on the role of heredity or specific environmental factors in the cancer process.

Physicians may be able to identify non-cancerous disorders that occur consistently within a cancer-prone family, the NCI scientist suggested. Family histories may reveal consistent evidence of genetic skin disorders, chromosomal abnormalities, defects in structural development, immune defects, enzyme deficiencies, or characteristic blood protein patterns.

(more)

Small familial risks among adults are well documented for cancers of the breast, stomach, colon, the inner lining of the uterus, prostate, lung, and melanoma. In children, the risk is slightly increased for siblings of patients with leukemia, brain tumors, and several solid tumors. The development of cancers at younger ages in cancer-prone families than among the general population suggests the influence of hereditary factors in these cancers, Dr. Fraumeni said.

Genetic influence in cancer development thus may be more visible in families in which there is evidence of cancer-related syndromes. Medical examinations of a particular family should include young adults and children, the NCI scientist emphasized.

The occurrence of cancer should also be traced for as much of the family tree as possible. Exhaustive search will help identify disorders that may occur together in the same individual but often are scattered throughout the family tree, he concluded.

#

HUMAN BODY--The mature human body is the end result of nearly 20 years of growth. Each individual begins as the product of two cells and eventually is made up of 100,000 billion cells, according to the National Institutes of Health. The most rapid and crucial period of growth in the human being occurs in the nine months before birth.

#

Research Advances

## FLUORIDE IN WATER IS MORE EFFECTIVE THAN IN FOODS

Tooth decay in newly-weaned rats infected with a human, decay-causing organism is reduced more effectively when the animals drink water containing sodium fluoride than when the animals eat the same amount in food, according to investigators at the National Institute of Dental Research (NIDR).

As in humans, fluoride prevents rat tooth decay more on smooth tooth surfaces than on irregular, deeply grooved, chewing surfaces according to Suzanne Amsbaugh who reported the findings to members of the American Association for Dental Research in New York on April 6, 1975. In her experiments, decay decreased as the concentration of fluoride was increased in food or drink of matched groups of rats. However, in water as little as 2.5 parts per million (ppm) of fluoride reduced the number of decayed areas on smooth surfaces to about a half of the number developed by animals that received no fluoride. An equivalent low intake of fluoride in food brought about approximately an eighth as great a reduction in decay on these surfaces.

Because the rats consumed twice as much water as they did of the dry, high-sugar diet used to encourage decay, the scientists had to add twice as much fluoride to food as to water to assure equal consumption of the protective salt. Miss Amsbaugh noted that sodium fluoride, unlike many forms of fluoride in natural animal diets, is soluble and readily absorbed. Therefore, if fluoride's protective effect were purely internal, both groups of rats should have benefited equally since they consumed the same total fluoride regardless of whether they ate or drank it. The challenge to the teeth was uniform because all animals got an identical high-sugar diet, and bacterial

(more)

sampling showed that the same human strain of *Streptococcus mutans* continued to infect them throughout the 56 days of the experiment.

These experiments support previous findings from NIDR's Dental Caries Program which showed that fluoride's strongest protective effect occurs in the mouth when that substance is constantly available in drinking water.

#

ARTERY HARDENING--Every artery throughout the body is subject to hardening, but the most often and most seriously affected vessels are the largest arteries, such as the aorta; the coronary arteries, and the arteries that feed the brain and kidneys. Arteries may harden in one part of the body more rapidly than in other areas, according to the National Institutes of Health.

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CARDIOVASCULAR SYSTEM--The body's circulatory system--also called the cardiovascular system--is made up of the heart and the arteries, capillaries, and veins. The heart contracts about 70 times each minute, pumping oxygen- and food-rich blood into all regions of the body to nourish the muscles and tissues, according to the National Institutes of Health.

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EARLY START--Hardening of the arteries may actually begin in early youth, perhaps even at birth. How troublesome it eventually becomes varies with each individual who has it. Some escape any consequence of the condition whatsoever. Others develop some symptoms, but with proper medical care continue normal and productive lives, according to the National Institutes of Health.

#

Research Advances

## LESS TOOTH DECAY NOTED IN STUDENTS GIVEN FLUORIDE

A National Institute of Dental Research (NIDR) scientist has reported interim results of a study which showed that children who chewed two fluoride tablets each school day over a period of nearly five years had about 30 percent less new tooth decay than comparable children in the same school who did not receive a fluoride-containing tablet.

Speaking in New York before the American Association for Dental Research in April 1975, William S. Driscoll, D.D.S., of the NIDR National Caries Program, said the study is being conducted in Wayne County, North Carolina, where the drinking water contains insignificant levels of fluoride.

Dr. Driscoll reported that over 1,000 children in the first and second grades were examined in October 1969 to determine the number of decayed tooth surfaces each child had before the test began. The children were then separated randomly into three comparable groups. The control group of children chewed a tablet without fluoride, rinsed their teeth for 30 seconds with the resulting solution and then swallowed the material.

The second group followed an identical procedure with an acidulated phosphate-fluoride tablet containing one milligram of fluoride. Children in the third group were given two of the fluoride tablets apiece, but the second tablet was taken at least three hours after the first. Tablets were given to all children each school day.

At the end of 55 months, the teeth of the 529 remaining children who had participated in the program since it started were re-examined. The children in the control group experienced over five new decayed surfaces.

(more)

Those youngsters who chewed one daily fluoride tablet averaged 20.8 percent fewer decayed surfaces, while those that chewed two tablets a day averaged 30.1 percent fewer decayed surfaces. The protection was found to be better in teeth that erupted during the test period than in teeth that were already erupted when tablet administration began. A final evaluation of the procedure will not be available until at least one more year of tablet administration has been completed.

Dr. Driscoll notes that fluoride tablet administration as a method of protecting against tooth decay takes very little school time and is inexpensive. Since it can be supervised by teachers, it does not require professional dental manpower; also, the tablets are not as likely to be forgotten as is often the case when tablets are administered by parents in a home-based program. Dr. Driscoll considers a school tablet program to be a feasible way to bring some of the benefits of fluoride to those children who live in areas where fluoride levels are too low to provide tooth protection. He emphasized, however, that continual exposure to about one ppm of fluoride in drinking water is still the best available public health method of preventing tooth decay.

#

LEUKEMIA--Leukemia is cancer of the blood-forming organs and is characterized by uncontrolled production of abnormal white blood cells. Leukemia may strike at any age, develops each year in about 19,000 Americans, and kills about 15,000, according to the National Institutes of Health.

#

Research Advances

## IMMUNOLOGICAL REACTIONS TO FOODS MIGHT CAUSE SOME ADULT TOOTH LOSS

The ability of corn and nut extracts to induce immunological reactions on the part of human white blood cells adds substance to a long-held idea that foods probably contribute at times to periodontal problems which cause adults to lose sound teeth.

The immunological findings of a group of National Institute of Dental Research scientists were reported on April 5, 1975, by William H. Radentz, D.D.S., to the American Association for Dental Research meeting in New York. He added that the leukocytes, when separated from the rest of the blood and maintained for about a week in culture fluid containing corn extract demonstrated a very rapid proliferation as compared to those lymphocytes not exposed to corn products. Black walnut, pecan, and almond extracts also stimulated these white cells non-specifically.

Dr. Radentz explained that one type of immunological reaction--the enlargement and multiplication of leukocytes--occurs when some foreign antigenic substance to which the donor of the white cells is sensitive or allergic is added to the culture fluid. However, other substances will non-specifically stimulate all lymphocytes regardless of previous exposure. These materials, often derived from plants, are called mitogens because they engender mitosis or cell division in all lymphocytes. Known mitogens were compared with the corn extracts for their effects on leukocytes. The scientists took samples of blood from healthy adults, and some known to be sensitive to corn. Comparison of these leukocyte reactions, they assumed, should indicate whether the reaction to corn extract would be limited to people with allergies or could

(more)

occur in the population at large.

The amount of response of a sample of leukocytes to any antigen or mitogen, Dr. Radentz said, is measured by a scintillation counter which records the amount of radioactive thymidine which has been taken up by dividing cells. Only during mitosis is thymidine incorporated in the cells, therefore they are exposed briefly to this material and prepared for counting. Any increase in radioactivity over that found in untreated samples of the same blood demonstrates the number of leukocytes which have been stimulated.

Another step in the study that Dr. Radentz reported showed still more potential for tissue harm. When some of the culture fluid removed from food-stimulated leukocytes was put into one side of a special chamber divided by a fine filter, another type of cell (monocyte) in the other side of the chamber was stimulated to migrate through the filter because it was attracted by a chemical substance in the culture fluid. Culture fluid from unstimulated leukocytes lacks this attracting substance. These molecules released by stimulated leukocytes have not yet been identified, but are called lymphokines as a group because they are biologically active.

According to the scientists, some lymphokines are known to make blood vessels leaky, some attract scavenger cells, and others cause a variety of immune reactions including severe, localized, tissue damage. This is why their experimental leukocyte reactions have led the investigators to believe that corn hulls, nut particles, and possibly other foods as well, might cause local destruction of gum tissue, especially when these foods lodge in crevices

(more)

around teeth. The scientists know of no other positive identification of any possibly damaging foods, although many clinicians have long suspected that food is involved in periodontal disease.

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*The National Institutes of Health supports medical research into all stages of human life. By contacting the NIH News Branch, editors can obtain current information about scientific investigations into various diseases.*

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Research Advances

## SUCCESSFUL FREEZING AND BIRTH OF RABBIT EMBRYOS REPORTED

The successful freezing and birth of rabbit embryos was reported in the January 1975 issue of *Experimental Cell Research*, a Swedish publication.

The article, entitled "Survival of Frozen Rabbit Embryos," was written by Harvey Bank, M.D., assistant professor of pathology at the Medical University of South Carolina, and Ralph R. Maurer, Ph.D., of the Environmental Toxicology Branch, National Institute of Environmental Health Sciences (NIEHS).

Previously, with the exception of mouse embryos, only single cells had been frozen. The rabbit embryos used in Drs. Bank's and Maurer's research are considerably larger and more sensitive to change than their mouse counterparts, representing a cryobiological advance toward more complex systems.

Multicellular systems are more difficult to work with since these more complex systems differ from one another in their response to freezing. New procedures were needed for successful freezing and survival of frozen rabbit embryos.

The effect of various cooling and warming rates, thawing procedures, and other variables on the survival of Dutch-belted rabbit embryos was determined. When most favorable factors were reached, 65 percent of the frozen embryos developed in culture.

Some of these fetuses developed into live offspring when reimplanted to a foster mother. These baby rabbits were normal in every way, and eventually gave birth to live offspring of their own.

Results should be valuable in many ways, according to Drs. Maurer and Bank. Preservation of these embryos facilitates transfer of specific strains

(more)

of experimental animals between laboratories and makes available large numbers of embryos for simultaneous experiments in different laboratories.

The response of embryos to freezing could aid understanding of the responses of complex tissues to freezing. Also, the relative sterility of early embryos may eliminate quarantine requirements or might serve to introduce specific strains into a sterile environment.

Drs. Bank and Maurer recently reported these findings with rabbit embryos to a workshop in Bar Harbor, Maine, sponsored by several international research organizations including UNESCO.

In further studies, Dr. Maurer and J.K. Haseman, Ph.D., Environmental Biometry Branch, NIEHS, using an optimization procedure and morula staged embryos, reported *in vitro* development of 83 percent for frozen and thawed rabbit embryos.

At the Seventh Annual Meeting of the Society for the Study of Reproduction held in Ottawa, Canada, they reported these results and the fact that one-fourth of the frozen embryos developed to full-term fetuses.

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HYPERTENSION--Hypertension, or high blood pressure, afflicts at least 23 million Americans, reports the National Institutes of Health. High blood pressure increases a person's risk of having a heart attack, stroke, or developing kidney disease.

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Photo Feature

# NIH SUPPORTS THREE CENTERS FOR HEAD INJURY RESEARCH

Research in head injury is a major interest of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), which is currently supporting three Head Injury Research Centers, as well as 13 related research projects and an intramural program at the NIH Clinical Center.

Scientists at the NINCDS-supported Head Injury Research Center at the Cincinnati General Hospital are studying the effects of intra-cranial trauma on systemic function. Brain injury and systemic disturbances often "feed" each other, as in cases where the injury causes pulmonary edema, which in turn causes lack of oxygen in the brain, compounding the damage. Sometimes, brain injury causes release of antidiuretic hormones, which adds to the problem of water retention (edema). The Cincinnati scientists are approaching the overall problem in both aspects.

*Robert L. McLaurin, M.D. (right), and James A. Mosso, M.D., of the Head Injury Research Center at the Cincinnati General Hospital, examine a patient who suffered a severe head injury. Continuous monitoring of intracranial pressure is studied. (NIH Photo #1383)*

Researchers at another NINCDS-supported center at the University of Chicago are studying the ultrastructural, biochemical, and physiologic changes that

(more)

Head Injury (Cont'd)

occur during head injury. The scientists are measuring changes in phospholipids, gangliosides, etc. This group is seeking to determine the cause of an immediate decrease in blood flow--the result in several types of head injury. They have found that dymethyl sulfoxide reduces swelling of spinal cord and brain tissue in trauma in dogs.

Scientists at the center at the University of Texas Medical Branch, Galveston, have worked out a practical method for continuous monitoring of intracranial pressure in head injury patients. They use a transducer inserted through a small hole in the skull. Sometimes vital signs such as heart rate and respiration are affected by the methods used to measure them, and the scientists are seeking to minimize this "perturbation response" by use of automatic monitoring equipment.

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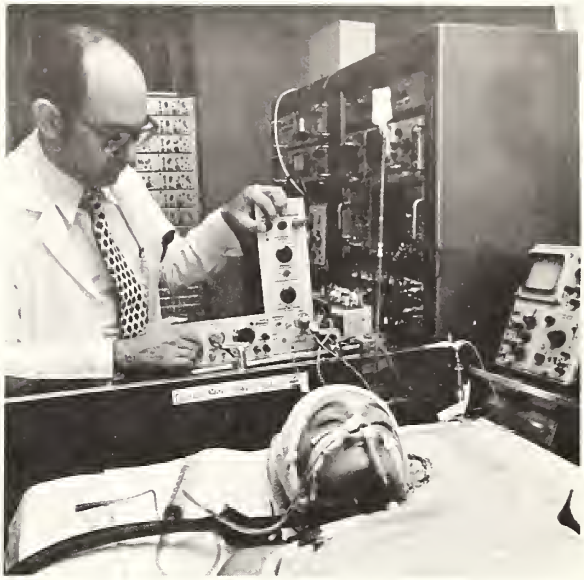

*Robert G. Grossman, M.D., of The University of Texas Medical Branch, Galveston, demonstrates equipment used in measuring intracranial pressure and brain activity on a head injured patient. (NIH Photo #1384)*

*John F. Mullan, M.D., of the University of Chicago, examines an X-ray of a head injury patient. (NIH Photo #1385)*

Photo Feature

## NIAMDD GRANT TO U. OF MICHIGAN WILL EXPAND PSORIASIS RESEARCH

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has awarded a $294,779 grant to establish a multidisciplinary program to expand on-going fundamental and clinical research efforts in psoriasis, a disease that is both physically and socially crippling to millions of Americans.

The enlarged program, located at the University of Michigan School of Medicine, Ann Arbor, will be headed by John J. Voorhees, M.D., professor and chairman of the Department of Dermatology.

The broad-ranging studies will combine the efforts of investigators in several university departments, and will include research in the fields of dermatology, biochemistry, pharmacology, pharmacy, and anatomy.

The investigations will place particular emphasis on the role of cyclic nucleotides in the control of epidermal proliferation, and will also initiate studies of other facets of the disease. This will be an extension of the observation made by Dr. Voorhees and his co-workers concerning cyclic nucleotide levels in psoriatic skin. This group was the first to describe altered hormonal controls (cyclic AMP) in the skin of patients suffering from psoriasis.

In addition, within the framework of the expanded program at the University of Michigan, a collaborative project will be carried out at the University of Utah. This project will be directed toward the detection of cell-mediated immunity in psoriasis. An attempt will be made to formulate an *in vitro* model of psoriasis utilizing transplantation of normal and psoriatic skin to germ-free congenitally athymic (nude) mice. The University

(more)

of Utah program will be under the direction of Gerald Krueger, M.D.

Nude mice are born without a thymus gland, and this makes them ideal for grafting human psoriatic skin, according to Dr. Krueger. The thymus acts as the body's center for disease control; when it is absent, the body is not able to reject a skin graft.

Since these mice have no immune system to establish longevity, they must be bred and raised in a germ-free environment. This sterile environment allows them to grow much larger than normal mice, giving researchers a larger skin surface on which to work.

The Utah researcher said a special machine is used to remove psoriatic skin from volunteers for grafting onto the mice. Interestingly, the skin appears to lose its psoriatic scale when grafted, although the condition is still present, as shown by its microscopic appearance, he said.

Through this expansion of research in the area of psoriasis, the flow of new scientific findings from the laboratory to the practitioner will be expedited. Other centers of dermatology conducting psoriasis research that is supported by NIAMDD are located at Harvard Medical School, the University of Miami School of Medicine, Temple University School of Medicine, Yale University School of Medicine, Duke University School of Medicine, Stanford University School of Medicine, and the University of Michigan School of Public Health.

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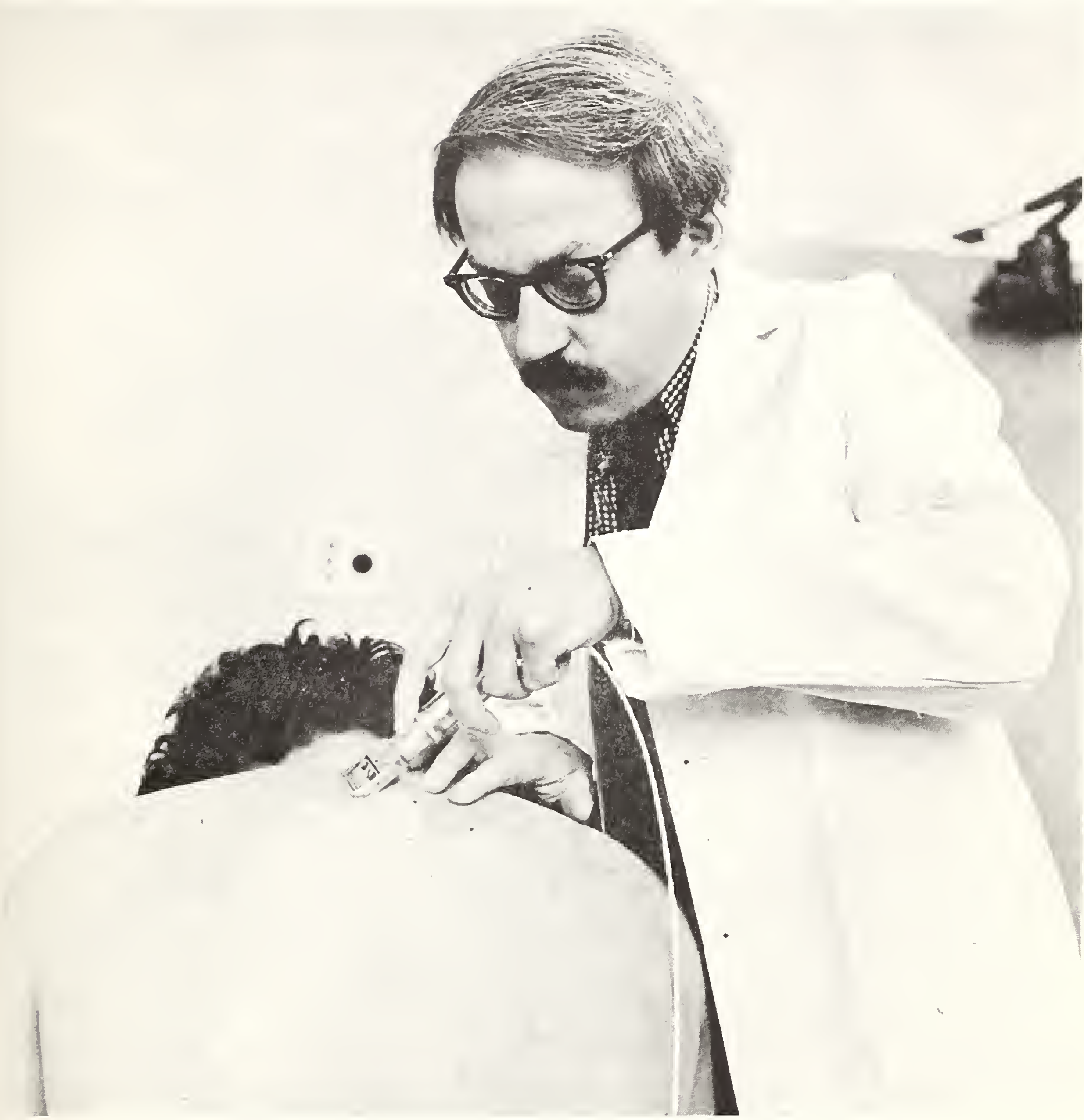

*John Voorhees, M.D., uses a keratome to remove a thin sample of tissue from a lesion on the back of a psoriasis patient. Preserved immediately in liquid nitrogen, the sample is later analyzed for minute quantities of cyclic AMP and cyclic GMP. University of Michigan research has shown that the cyclic AMP/cyclic GMP ratio may well be central to the beginning and/or continued presence of a psoriasis lesion. (NIH Photo #1386)*

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News Feature

## CELL STUDIES ADVANCE BIOMEDICAL RESEARCH

The cell is the basic building block of all living organisms, both plants and animals. Living cells commonly range in size from about five micrometers to 100 micrometers. (Since there are about 25,000 micrometers in one inch it would take about 2000 typical cells lined up end-to-end to equal one inch.) All tissues and organs consist of cells; it has been estimated that the human body contains about 26 trillion cells.

Biochemists at the National Institutes of Health and elsewhere have been studying cell composition for many years, and have discovered that cells consist mostly of three types of chemicals: proteins, carbohydrates, and lipid fats. Each of these are complex molecules consisting of subunits. The smallest subunits of carbohydrates are simple sugars such as glucose. The smallest subunits of proteins are amino acids of which there are about 20 different kinds. Carbohydrates and one type of lipid (triglycerides which are fats and oils) are the source of much of the energy of the cell.

There are hundreds of different proteins in each cell. Many proteins are enzymes which serve as catalysts to accelerate the chemical reactions that occur in cells. These chemical reactions, the mechanisms by which the cell synthesizes all of its own constituents from the nutrients it obtains and the way in which the cell obtains the energy necessary to do this, have been until recent years the major topic studied by biochemists and other biological scientists.

During this period, the functioning of the whole body and its organs has been the province of physiologists and other biomedical scientists.

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These scientists studied such things as the changes in the composition of blood when it passed through the kidney, or the force and rate of the contractions of the heart and how they could be affected by drugs. Cells were recognized as the functional unit of the body organs but it was rarely possible to relate the studies of the biochemist, carried out at the molecular level on extracts of tissues, to the observations of the physiologist, carried out with whole organs or intact animals. The cell was a "black box."

Then slowly, as the consequence of a number of developments culminating in the 1960s, things began to change. With the invention of the electron microscope and the development of techniques of tissue preparation, it became possible to visualize the internal structure of cells. The electron microscope allows one to "see" structures one million times smaller than can be discerned by the unaided eye and 2000 times smaller than can be seen through the light microscope.

It was then definitely established that the cell was not just a nucleus immersed in a "soup" of cytoplasm all enclosed within a cell wall but, rather, a highly organized system of organelles, membranes, and other structural elements which separated the interior of the cell into many compartments. At the same time, other scientists discovered that, when suspensions of broken cells were subjected to a series of different centrifugal forces, it was possible to separate these intracellular organelles from each other and thus obtain highly purified preparations of each. It was then soon found that each of the intracellular organelles carried out specific metabolic activities. Like the organs of the body, each of the cell organelles has a characteristic shape, size, and function.

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Cells (Cont'd)

Many of the intracellular organelles, but not all, share one feature; they are membrane systems or are structures enclosed by membranes. Although each of these membranes is different in its essential features, the membranes have broad similarities. Membranes are extensive structures in two dimensions but are very thin, about 10 nanometers wide (there are about 25 million nanometers in one inch). Proteins and phospholipids (a type of lipid) make up most of the membranes of the cell, and cholesterol is an important component of the external cell membrane. Many of the membrane proteins are enzymes and many of the important metabolic reactions of the cell occur in membranes.

These studies, by many scientists over a period of 20 years, have revolutionized biomedical research. It is now possible to study the structure, composition, and function of each of the subcellular structures and, in so doing, to understand for the first time the functioning of cells. It is also possible to investigate the details of the interactions of cells with each other. It is this cooperative interaction among cells that is responsible for organ function. With the certainty that disease must originate in abnormal cell function, this is a period of great promise.

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CLOGGED ARTERIES--Hardening of the arteries sets the stage for many strokes by clogging arteries carrying blood to the brain. The damaged artery or arteries may be located either inside the brain or in the neck, according to the National Institutes of Health.

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Photo Feature

# RESEARCHERS CONNECT NERVE AND MUSCLE CELLS

As part of a program to begin to understand how the brain functions, researchers at the Neurobiology Laboratory at The Salk Institute have recently succeeded in forming a working nervous connection between a small piece of spinal cord and a muscle cell grown in culture.

Stephen Heinemann, Ph.D., Yoshiaki Kidokoro, M.D., Ph.D., and David Schubert, Ph.D., and their colleagues are studying so-called clonal cell lines--populations of cells that have descended by repeating growth and division from individual cells. Each cell in a clonal cell line is therefore exactly like its fellows, providing the researchers with the mass of several million identical cells that is necessary if their biochemistry is to be studied.

*Dr. Stephen Heinemann cultures cells from the nervous system. (NIH Photo #1387)*

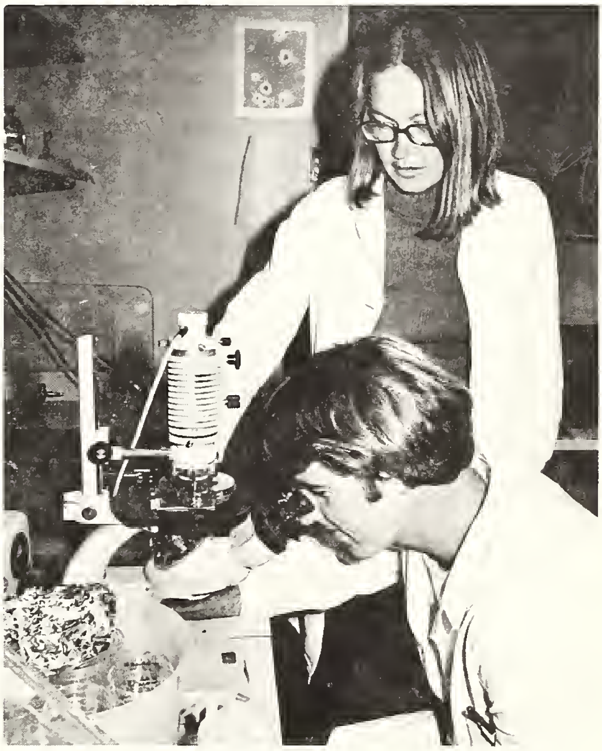
The researchers at The Salk Institute are seeking to understand the overwhelmingly complex human brain by reducing the problem to the simplest possible level: that of its individual cells and the interactions of one cell with another. While it is not yet

(more)

possible to study the connections (synapses) that one nerve cell makes with another, the nerve-muscle cell synapses can be investigated by spearing the cells with tiny electrodes.

The neurobiology group has developed several new clonal cell lines derived both from muscle cells and from brain cells. These programs are now well advanced, with a number of new nerve and muscle clonal cell lines now established and characterized.

These studies of the brain are supported by the National Institute of Neurological and Communicative Disorders and Stroke.



*Working in laboratories at The Salk Institute are Yoshiaki Kidokoro, M.D., Ph.D. (left photo), David Schubert, Ph.D. (seated in right photo), and Helgi Tarikas Jobe. (NIH Photo #1388 and #1389)*

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News Feature

## STREP DISEASES ARE COMMON, BUT STILL VERY MYSTERIOUS

Streptococcal diseases are the most common bacterial infections in humans, yet huge gaps in our knowledge of them remain. The streptococcus organism was first identified 100 years ago, but problems still exist in the diagnosis, treatment, and prevention of the illnesses it causes.

Diagnostic tests are not completely reliable, and frequently, can only indicate the presence of a previous infection. Treatment, in most cases, consists of penicillin, but the increasing number of patients with penicillin allergy necessitates the search for new drugs. Although there were over 400,000 cases of strep throat and scarlet fever reported in the U.S. in 1972, no vaccine is commercially available.

A limiting factor in progress against streptococcus is the lack of a common denominator for describing the disease-causing potential of the organism. The interaction between streptococcus and the humans is astonishingly complex, as might be expected from the many areas of the body which the bacterium affects.

The primary locations of Group A streptococci, or strep, is the respiratory tract, where they cause sore throat or scarlet fever, and the skin where impetigo is the common infection. Invasion of the bloodstream, usually by streptococci other than Group A, results in bacteremia and subacute bacterial endocarditis. Urinary tract infections can be caused by two groups of strep, one of which also affects the central nervous system in babies born of infected mothers. Permanent damage to the heart and kidney can result from rheumatic fever and acute glomerulonephritis, two possible after-effects of

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strep infections.

Rheumatic fever (RF) is an insidious disease which may develop in three percent of those who have had a strep throat and have not had proper antibiotic treatment. A great deal of concern is generated by this disease since permanent heart damage occurs in 25 percent of rheumatic fever patients. Scarring and distortion of the heart valves is frequently unnoticed until years later when the patient is seriously incapacitated or experiences a heart attack. By this time, the patient may not even recall having had a previous case of acute rheumatic fever.

The peak occurrence of RF coincides with that of strep throat, that is late winter and early spring. Although rheumatic fever is largely preventable by proper doses of penicillin, the incidence of the disease is almost as high today as it was a decade ago. Yearly estimates are 50,000 to 100,000 cases but these figures are probably low since physicians are no longer required to report occurrences of the disease to the Public Health Service.

RF is basically an inflammation of the small blood vessels. The most common symptoms are fever and inflammation of the joints. Swelling and pain seem to migrate from joint to joint. Inflammation of the heart (carditis) may lead to murmurs, enlargement of the heart, and congestive heart failure. Sydenham's chorea, which is rapid, purposeless, non-repetitive movements of the muscles, appears late in the disease.

Carditis is the only aspect of this disease which does not disappear within a few months. Unique lesions of the heart muscle, known as Aschoff's bodies, cause scarring and distortion of the valves which reduces the pumping efficiency of the heart. To compensate for this, the heart may enlarge.

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Damage may remain unnoticed until the heart valves no longer function properly.

The major reason why the heart can be damaged so stealthily is that, in many instances, RF is a difficult diagnosis to make. There is no specific test for rheumatic fever, only tests that confirm a previous strep infection. Not all cases of RF follow the classic example and the symptoms, such as fever and joint pain, are signs of a variety of ailments.

There is no specific treatment for RF. Bed rest, usually for several months, is generally prescribed. Aspirin and steroids remove the more obvious complaints, and penicillin is administered to eliminate any remaining strep infection.

Susceptibility to a recurrence of rheumatic fever seems to depend on the severity of carditis. Patients who do not develop carditis have few recurrences. Penicillin should be administered prophylactically to RF victims with the length of time that they receive the drug based on the degree of heart damage. Those with severe cardiac damage may receive penicillin for the rest of their lives.

Current speculation views RF as an unusual immunologic response of a person to the strep organism. Cross-reactivity between strep antigens and human heart muscle has been demonstrated, while deposits of immunoglobulins and complement, important components of the immune response, have been found on postmortem rheumatic hearts.

Acute glomerulonephritis (AGN) is a serious disease characterized by inflammation of clusters of blood vessels in the kidney called the glomeruli. In large families it is common to see multiple cases of acute glomerulonephritis develop within days of one another. Epidemics have also been reported.

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Most often, the disease is the aftermath of infection by a kidney-damaging strain of Group A beta-hemolytic streptococci. AGN occurs 18 to 21 days after a strep skin infection or 10 days following a strep throat.

Usual symptoms of AGN are loss of energy, pallor, facial puffiness--particularly of the eyelids--and bloody or coffee-colored urine. However, not all of these signs need be present for AGN to occur. There is a wide range in the degree of symptoms. The acute phase of the disease lasts from three to four weeks and complications can only be treated successfully if caught early. A decrease in urine secretion is responsible for edema, which is fluid retention in tissues, with subsequent hypertension and renal failure. If the edema is significant, congestive heart failure may occur.

The earliest and most sensitive indicator of nephritis is a decrease in the level of a serum protein, complement. Other tests are indicative of a previous strep infection, such as measurement of antibody titers to extra-cellular products, in particular, streptolysin O.

There is no specific treatment for glomerulonephritis. Bed rest and a diet low in salt and protein can be prescribed if there is decreased renal function. After a few weeks, there is usually an increase in urine secretion and the body's chemistry returns to normal. Improvement is gradual, with complete recovery in less than a year. Total recovery occurs in 85 to 95 percent of affected children and in 50 to 75 percent of adults.

As with rheumatic fever, AGN is currently believed to be caused by the body's immune response to streptococcus. The decrease in complement level, an indication of an immunologic reaction, supports this hypothesis. The long

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delay in onset, suggestive of the development of an immune response, and the discovery of antigen-antibody complexes in the glomerular lesions further support this theory.

At the Scripps Clinic and Research Foundation, La Jolla, Frank J. Dixon, M.D., a grantee of the National Institute of Allergy and Infectious Diseases, has been responsible for much of the definitive work implicating the immune complex of antigen-antibody and complement as the cause of tissue damage in AGN. He has shown that there are two different mechanisms which can operate in human AGN.

In some cases, the patient produces antibodies against his own kidney antigens. In others, the patient produces antibodies which react with other antigens that are circulating in the blood and form antigen-antibody complexes which are then trapped in the kidney. In both cases, immune complexes are concentrated in the glomeruli of the kidney where they can cause inflammation. Either of these mechanisms can cause a severe, rapidly progressive, destructive disease or a mild, slowly developing disorder.

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EMPHYSEMA--Life expectancy is reduced by circulatory complications combined with emphysema. Especially serious are such added problems as right-heart "overwork" owing to high blood pressure in the pulmonary blood vessels and an abnormal increase in the number of red blood cells, according to the National Institutes of Health.

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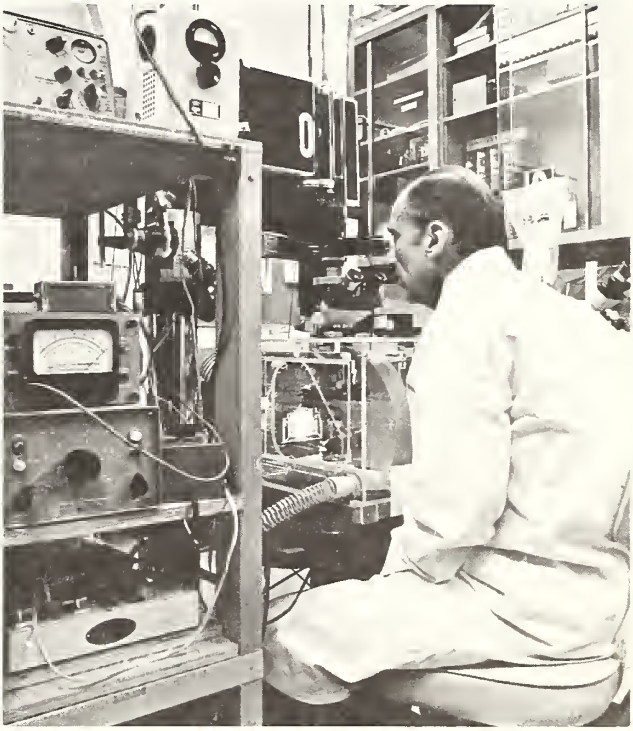
Photo Feature

# RESEARCHERS TAKE MOVIES OF SALIVARY GLAND CYCLE

In an effort to understand how the secretory cell functions, scientists at the Center for Research in Oral Biology, University of Washington, Seattle, use a combination of differential interference light microscopy, time-lapse cinemicrography, and a computer to plot the time span of certain significant events in the salivary gland secretory cycle.

Small bits of dissociated gland tissue are placed in a microchamber under the microscope with its attached time-lapse camera. By using cells that are already full of secretory granules and then activating them with isoproterenol, a stimulating drug, the egestive (or ejecting) phase of the secretory cycle can be recorded by time-lapse cinemicrography. The camera is set to take a frame every second. The resulting film is then analyzed by tracing every sixth frame onto coordinate paper and measuring features such as lumen size and number of granules. With this information, the computer will produce a chart showing the exact timing and degree of change in the cells.



*With this cinemicrography apparatus, Dr. Arnold Tamarin takes motion pictures of cells or organisms as they go through phases of the secretion cycle, replicate, and perform other functions that may take hours or days. A 16 mm camera is mounted on a differential interference light microscope. The camera can be pre-set to take a frame every second or at longer intervals. (NIH Photo #1390)*

Salivary Gland (Cont'd)

Arnold Tamarin, D.D.S., professor of oral biology, indicates that with this technique it is possible to observe the loss of secretion granules in individual cells (as the granules spill their contents) in response to isoproterenol. The majority of the cells appear to release their granules (whose contents flow into the lumen) in 25 minutes, once the initial response to the stimulus begins. The lumen is the space into which the initial secretion passes on its journey through the salivary ducts that eventually empty into the mouth. The phase of greatest activity is in the first 15 minutes when the lumen swells to its greatest size. After 15-18 minutes, the release of the granules is slower and the lumen becomes smaller. After 25-30 minutes, a steady state is reached.

According to Dr. Tamarin, "To know *how* the secretory cell functions, you first have to know exactly *what* it does, and *when*, in relation to its own time schedule as expressed in its life history. You also have to know the cell's changing form, or morphology, and how this structure relates to what the cell is doing at any given time."

The study indicates, among other things, that not all acinar (secretory) cells in a gland "turn on" at the same instant to begin releasing their products. Dr. Tamarin's longitudinal kinematic studies, supported by the National Institute of Dental Research, show the sequence of cellular events and allow for their quantitative analysis. This contrasts with cross-sectional studies which tend to obscure the unsynchronized activity of individual cells.

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Salivary Gland (Cont'd)

*Dr. Ruth Pickering is pipetting a suspension of dissociated salivary gland cells for biochemical analysis and observation via cinemicrography. (NIH Photo #1391)*

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News Feature

## MYASTHENIA GRAVIS ATTACKS NERVE AND MUSCLE JUNCTION

Tired after a day's work? So is everybody else occasionally. But for approximately 30,000 Americans who have myasthenia gravis (MG), tiring easily is a way of life.

People with this disorder of the nerve-muscle junction tend to have difficulty in eating or talking, abnormal weakness of arms or legs, and often double vision. Myasthenia gravis attacks the point at which nerve meets muscle, stopping the electrical impulse before it can excite the muscle to contract. The disease can be effectively controlled in a large percent of cases, but without treatment it becomes progressively worse.

The cause of MG is still unknown. In most of the persons affected, muscles and nerves are normal. The disease is most common among those between 10 and 40 years of age. Climate, geography, or race are not controlling factors. There is no firm evidence that the disease is inherited. Though the condition may be present at birth in the child of a myasthenic mother, it readily responds to treatment.

The onset may be sudden, with extensive paralysis, but more often the early symptoms are slight, weakness being more apparent after exercise and at the end of the day. In severe cases the muscular weakness is constant. During an acute attack or crisis, even the muscles of respiration may fail to function.

Because of the wide variation in symptoms of the disease and the frequent periods when symptoms are slight or absent, extended observation is

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necessary for determining the best treatment in each case. Also, it takes time to establish an effective pattern of dosage for most drugs since too much or too little of some medicines can bring on an acute attack.

Today's research into MG includes a broad spectrum of programs conducted and supported by the National Institute of Neurological and Communicative Disorders and Stroke. Several new drugs are valuable in controlling the symptoms. Others have proven dangerous and are not recommended for use with MG. Surgery and X-ray in certain cases have resulted in improvement of the patient and are being evaluated further.

Myasthenia gravis is frequently associated with abnormal changes in the thymus. In some patients, removal of the thymus has been followed by marked improvement, but in others improvement has been transient or did not occur following thymectomy.

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COLLATERAL CIRCULATION--Nature has her own remarkable way of averting disaster even though the coronary arteries have started to harden--"collateral circulation." Neighboring arteries carry more blood than formerly to compensate for a narrowed vessel, and new arterial branches open up to help transport blood to where it is needed, according to the National Institutes of Health.

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COMPUTERS--Computers at the National Institutes of Health can monitor a post-surgery patient's heart rate and blood pressure 200 times a second.

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Photo Feature

# LOWERED PRIMATE EXPORTS PROMPT DHEW SUPPLY PLAN

Severe constriction of nonhuman primate export quotas by foreign countries has prompted the Department of Health, Education, and Welfare to take immediate action to assure that government-supported biomedical researchers will have an adequate number of laboratory primates to continue their studies.

India, Peru, and Colombia are responsible for nearly 80 percent of the U.S. primate annual imports.

In July 1973, the Government of India announced that the number of rhesus monkeys (Old World) permitted to be exported annually would be reduced from 50,000 to 30,000. This means a net of about half the anticipated supply for the United States. India has also warned of future reductions in the years to come, and is expected to reduce the quota to 20,000 annually for 1975-1976.

Peru ceased exporting New World primates in October 1973. Pending the initiation of a proposed conservation program, Colombia has recently stopped issuing primate export permits.

In 1974, the National Institutes of Health (through its Animal Resources Program, Division of Research Resources, and the Veterinary Resources Branch, Division of Research Services) instituted a domestic breeding program as part of the NIH National Plan for Rhesus Monkeys.

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Primates (Cont'd)

The report, compiled under supervision of staff officer Nancy A. Muckenhirn, Ph.D., contains a comprehensive overview of the primate situation in the United States. It conclusively confirms the opinions of many primatologists and biomedical scientists who are concerned with regard to the present dwindling supply of laboratory primates and the problem of maintaining adequate stocks in the future.

Further documenting the dwindling foreign supply, the report confirms that the total numbers exported to the United States from all countries decreased by 32 percent from 1964 to 1973.

The National Academy of Sciences report recommended the development of a national primate plan, including establishing domestic breeding colonies of commonly used species; improving trapping, holding, and shipping techniques and methods in countries of origin; establishing a system to facilitate multiple use of primates in research and establishing breeding colonies in the countries of foreign origin.

The National Academy of Sciences also recommended that the overall administration of this plan be guided by the National Institutes of Health.

Currently, there are ten NIH-supported rhesus monkey breeding contracts in effect. All contractors report satisfactory progress.

The Animal Resources Program of the Division of Research Resources is now reviewing contract proposals for the establishment of a squirrel monkey breeding program for extramural use.

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Primates (Cont'd)

Following this development, the DHEW Assistant Secretary for Health in October 1974 approved the formation of a departmental-wide Primate Steering Committee, with the National Institutes of Health serving as the lead agency. The purpose of this committee is to develop a unified plan to assure primate supplies for biomedical research activities.

The primary objectives of the Primate Steering Committee are to develop and implement a domestic breeding program to assure a supply of medically-important primates; assist in the development of primatology programs, including breeding, in certain South American countries (New World countries of origin) including Brazil, Colombia, and Peru; develop plan to implement goal of increasing from 60 to 100 percent the NIH Primate Research Centers' capacity to breed major primate species required for their research programs; and coordinate the use of primates for research in the United States, including the establishment of an allocation system if this becomes necessary.

It is anticipated that this committee will be expanded to include other Federal agencies using significant numbers of primates in their research programs.

Coincident with the establishment of the Primate Steering Committee is the issuance of the final report, NONHUMAN PRIMATES USAGE AND AVAILABILITY FOR BIOMEDICAL PROGRAMS. This special survey was conducted by the Institute of Laboratory Animal Resources of the National Academy of Sciences, under contract by the Animal Resources Program of the Division of Research Resources, National Institutes of Health.

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Primates (Cont'd)

*The squirrel monkey ranks second in importance as a major primate laboratory animal for biomedical research. The Animal Resources Program of the NIH Division of Research Resources has initiated a squirrel monkey domestic breeding program to augment the current NIH National Plan for Rhesus Monkeys. Major uses of the squirrel monkey are in metabolism, atherosclerosis, gallstone, and cancer virus studies. Because of its small size and ease of maintenance, the squirrel monkey is being used for many other general research activities. (NIH Photo #1392)*

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News Feature

## SCIENTIST EXPLORES BIOPHYSICAL ASPECTS OF RED BLOOD CELL AGING

How does the macrophage pick out old red blood cells that are "deteriorated" or "undesirable"? This question was examined by David Danon, Ph.D., at a recent Gerontology Research Center seminar.

Dr. Danon's laboratory has conducted extensive studies on the biophysical aspects of red blood cell aging over the past 15 years. He heads the Biological Ultrastructure Section of the Weizmann Institute of Science, Rehovot, Israel.

An internationally recognized electron microscopist and expert on red blood cells, Dr. Danon is President of the 10th International Congress of Gerontology to be held in Jerusalem, June 22-27.

In their research, the Israeli scientists assumed that the macrophage does not recognize enzymatic activity levels within a red blood cell as the signal to remove it from circulation after its 120-day useful life span.

Their studies point to the signs "read" by the macrophage as either a diminished ability of the cell to change form and return to its original shape without breaking (reversible deformability), or a reduced negative charge on the old cell.

Data collected in Dr. Danon's laboratory favor the reduced surface charge on the old cell membrane as the primary sign recognized by the macrophage.

It may not be the only sign, Dr. Danon added, since there are increased numbers of antigens on the old cell membrane. Therefore, he said, the reduced surface charge may help the macrophage get closer to the cell membrane where it recognizes the surface antigens newly available for interaction.

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The Center is part of the National Institute of Child Health and Human Development until the National Institute on Aging is in full operation.

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COMPUTER "DIAGNOSIS"--Scientists at the University of Michigan's Dental Research Institute have developed a computer program that aids orthodontists in deciding what treatment is necessary to correct malocclusion.

A 25-year accumulation of measurements of X-ray photographs showing skull growth at all ages for many types of faces has been stored in the computer memory.

An X-ray picture of a child with malocclusion, or better still, two pictures taken six months apart, can be compared with similar types in the memory bank. Within minutes the probable growth pattern is projected as a line drawing. Then, before he applies any braces, the dentist can see the effects of his proposed treatment. If the drawing is unsatisfactory, he can make the necessary changes until he gets the desired results.

This computer is also useful as a teaching tool. Young orthodontists can visualize general growth changes, characteristics of specific racial or family types, and patterns of development in patients with unusual hereditary or disease problems.

The computer is helpful with rarely-seen orthodontic problems. Its data banks have scientific information about thousands of skulls from prehistoric man to living patients. Thus, results of previous research aid the orthodontist in making diagnosis and treatment.

This research is funded by the National Institute of Dental Research.

#

News Feature

## NHLI SUPPORTS STUDIES OF RED BLOOD CELLS

The red blood cell provides an easily accessible model for studying physiologic mechanisms and metabolic controls common to many cell systems.

Red cells preserved outside the body (as in blood prepared for transfusion) depend on intact metabolism and membrane function for survival and function. Therefore, better understanding of the red cell membrane and enzyme systems is applicable not only to red cells and red cell preservation, but also to the understanding of the metabolism and preservation of other body cells, tissues, and organs.

The National Heart and Lung Institute (NHLI) supports studies on membrane structure, function, and intracellular metabolic activity.

Scientists are exploring the properties of red blood cells which contribute to their viability and which support their physiologic function in the circulation, e.g., oxygen transport and regulation of metabolism. Researchers are also investigating such physical properties of red blood cells as deformability, adhesiveness, and viscosity; physiochemical factors involved in the interaction of blood cells with one another and with their suspending medium; and investigation of biochemical, clinical, hematological, and genetic factors in diseases in which there is an inborn error in the metabolism of the red cells.

Other studies supported by NHLI are concerned with the problems of transport across cell membranes and relationship of chemical properties and functions to cell types, transition from fetal to adult characteristics of membrane transport, and effects of various agents and conditions on permeability.

#

## News Releases Issued

ASPIRIN STUDY--Recruitment of some 4,200 men and women, aged 30 to 69, who have previously experienced acute heart attacks (myocardial infarction) began in May at the 30 clinical centers participating in the National Heart and Lung Institute's Aspirin-Myocardial Infarction Study (AMIS).

The aims of the study are to determine whether and to what extent regular administration of aspirin (1 gram daily) over a three-year period will reduce mortality rates and reduce the threat of recurrent heart attacks or stroke in the study population.

A major factor in many heart attacks and most strokes is the formation of blood clots (thrombi) in the coronary arteries that nourish the heart muscle or in blood vessels supplying blood to the brain. Tissues "downstream" from the obstructed artery, deprived of essential nutrients and oxygen, may suffer extensive damage or destruction.

An estimated 1.5 million heart attacks and strokes, about half of them fatal, occur each year in the U.S. Thus scientists have been seeking effective means of preventing clotting complications of blood-vessel disease that are believed responsible for a high percentage of these disabling and frequently lethal events.

An early, probably critical event in the formation of an arterial blood clot is the aggregation, or "clumping" of blood platelets. Platelet aggregation is inhibited by a number of agents, including aspirin, and it is believed that such agents may confer some degree of protection against thrombosis in those at high risk of such complications. The AMIS is designed to test this hypothesis.

---

GRANT REGULATIONS--Proposed regulations governing grants awarded by National Heart and Lung Institute in support of projects for the prevention and control of heart, blood vessel, lung, and blood diseases were announced May 2 by Theodore Cooper, M.D., Assistant Secretary for Health.

Under section 414 of the Public Health Service Act the NHLI Director is empowered to make grants for projects to 1) demonstrate and evaluate the effectiveness of new techniques and procedures for the prevention, diagnosis, and treatment of these diseases; 2) develop and evaluate methods of educating health practitioners concerning these diseases; and 3) develop and evaluate methods for educating and motivating the public in methods for their prevention and control.

---

SPECIAL MONTH--Caspar W. Weinberger, Secretary, U.S. Department of Health, Education, and Welfare, has designated May as National High Blood Pressure Month.

The purpose of National High Blood Pressure Month is to focus national attention on a disorder that afflicts an estimated 23 million American adults, is the direct cause of some 20,000 deaths each year, and is a contributing factor in a great many of the more than 1,500,000 heart attacks and strokes--about half of them fatal--that occur each year in the United States.

Sponsors of National High Blood Pressure Month are DHEW, the American Heart Association, the American Medical Association, the American Hospital

(more)

Association, the American Osteopathic Association, the National Medical Association, and Citizens for the Treatment of High Blood Pressure, Inc.

In May and during ensuing months, the sponsoring agencies and more than 100 other participating groups--including private, professional, voluntary, state, and Federal organizations, as well as over 300 local groups--will take part in a national education and screening program.

#

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

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NEWS & FEATURES From NIH
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Building 31, Room 2B-10
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# PORTFOLIO

# AUTOMATED CLINICAL LABORATORY PROGRAM

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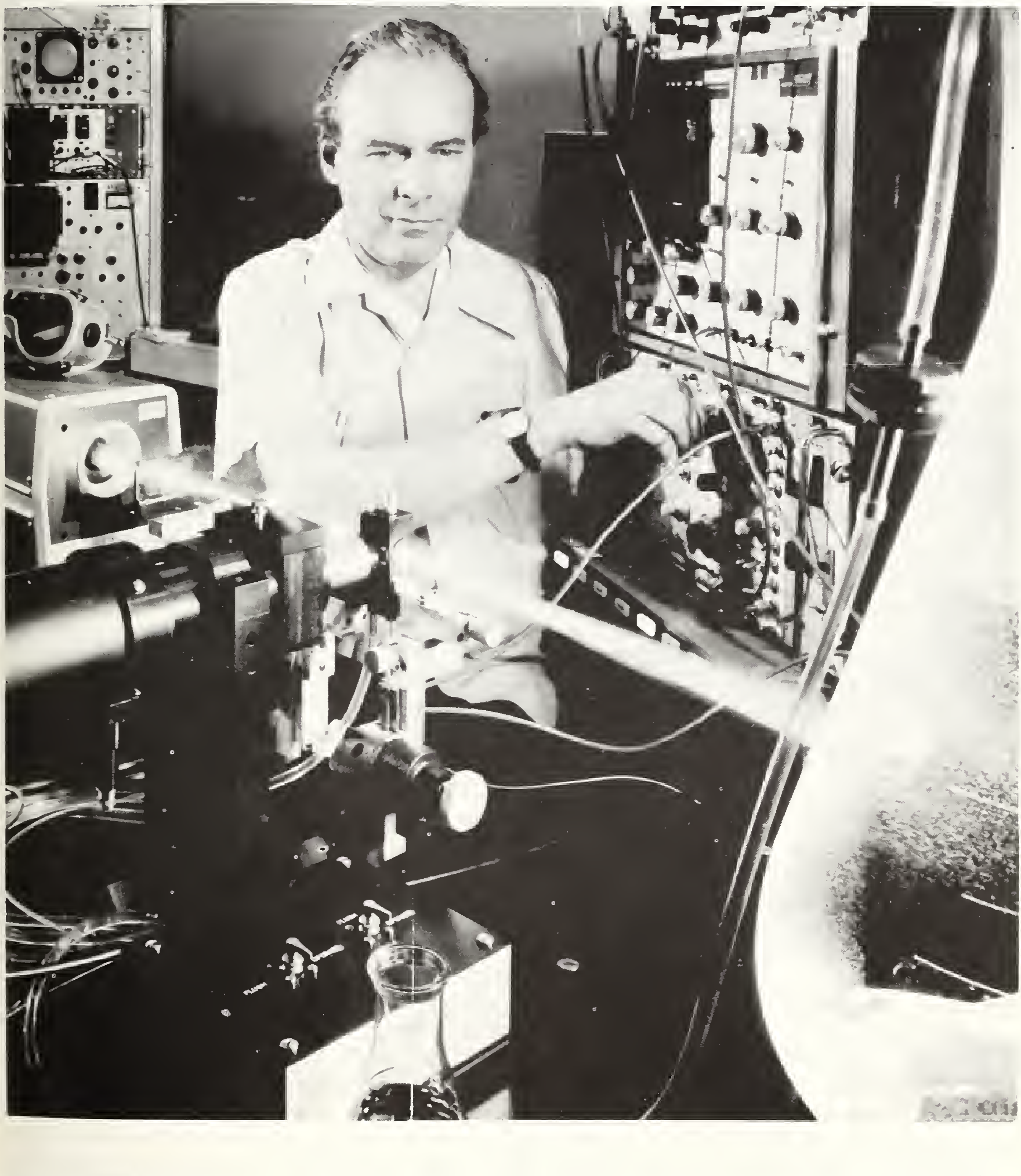


(See Page Nine)

MAY 1975

**NEWS&FEATURES FROM NIH**

NIH News Branch, Building 31, Room 2B-10, Bethesda, MD 20014, (301) 496-1206

Marc Stern, Editor

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

May 1975

## INTRODUCTION: NIH SUPPORTS RESEARCH IN THE AUTOMATION OF CLINICAL LABORATORIES

Clinical laboratories have the responsibility for providing a wide variety of tests that are crucial to the prevention, diagnosis, and treatment of disease. They are, in fact, a major funnel through which the benefits of modern medical knowledge reach the patient. The provision of adequate clinical laboratory service in the future will depend upon the development of more efficient methods, better instruments, and appropriately mechanized and automated technology.

To this end, the Automated Clinical Laboratory Program of the National Institute of General Medical Sciences currently supports research and development on new and refined types of separations techniques, new modalities for the measurement of biological substances, more sensitive instruments, and computer hardware and software suitable for the automated analysis of biological specimens. The major areas of concern to date have been: clinical chemistry, hematology, microbiology, and urine analysis. It would appear that by making progressive improvements in both the hardware and software now available, it should be possible in the next few years to increase by several fold the effective automation of clinical chemistry and hematology. An overall goal is to develop a modular, automated clinical laboratory system that can be adapted to benefit all sizes of hospitals from the small community hospital to the large university hospital complex.

This program is considered to have singular importance and high priority in the order of developmental work that must be undertaken to assure the country of a more adequate system for the delivery of health services. Public concern over our "health-care crisis" has increased significantly in recent years. This concern has been directed at the clinical laboratory as well as at other areas in the health-care system. Can the clinical laboratory be made more responsive to the needs of the patient? Can the clinical laboratory develop procedures that will allow the clinician to more readily take advantage of recent biomedical advances? Can cost per test be decreased? To provide answers to these and similar questions, the Institute feels that it is necessary to maintain a continuing, concerted effort toward developing advanced concepts and methods.

(more)

## PROGRAM DESCRIPTION

The Automated Clinical Laboratory Program presently includes four program projects and 55 regular research grants--all directed toward improving the state of the art in laboratory medicine.

The scope of this supported research ranges from basic analytical and biochemical studies to the application of computers for processing and reporting the large amount of data generated by today's clinical laboratories. Mechanization and on line automation, ranging from specimen examination to daily cumulative test results for the physician, has been developed for some clinical chemistry and hematology tests. Computer programs for microbiology which take into account the slow growth of micro-organisms obtained from laboratory specimens are now being explored.

In addition to grant support, contract support directed toward some of the more critical solvable problems in the clinical laboratory is available. These include accurate, direct methods for the determination of chemicals in blood, positive patient/sample identification systems, standard reference materials and methods, and the improvement of diagnosis for viral infections.

## NEW AREAS OF RESEARCH

Microcalorimetry--Although the fundamental theory of calorimetry has been known for many years, it has not been successfully applied to the field of clinical chemistry. With the advent of highly sensitive thermisters capable of measuring minute temperature changes, the development of microcalorimetry for chemical analysis now shows great promise. This technique could be especially effective for the assay of enzyme concentrations in minute samples of serum provided suitably purified substrates can be made available.

Fluorescence--The lack of specific appropriate physical chemical and physical optical knowledge of the behavior of fluorescent labels used in biological systems has probably been the principal reason that automated methods for the detection of fluorescent antibodies have not been universally accepted. A concerted effort in this direction may yield new tools for the analysis of constituents of biological materials.

Ion-Selective Sensors--Though recent progress in ion-selective membrane research has increased its potential for use in the clinical laboratory, actual implementation has been slow. If sensors of this sort are to be used as effective tools in clinical chemistry, it is essential that their operating principles and electrical and chemical limitations be clearly understood. To date, electrodes are available for the selective determination of approximately 20 ions. These sensors appear capable of performing continuous measurements and there is a strong likelihood that they will lend themselves to automated techniques. Research is ongoing in this area, but additional effort is needed if we are to achieve an adequate understanding of the function of these sensors.

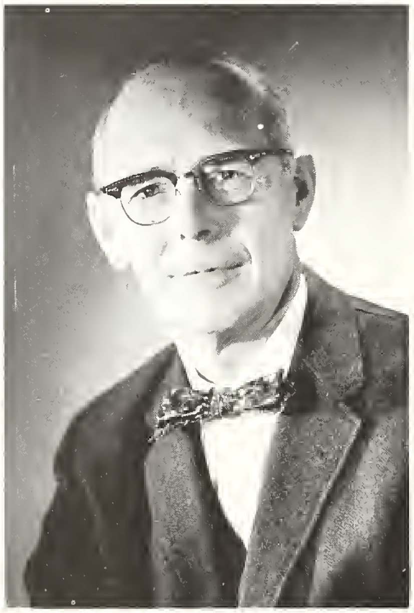
(more)

Feedback Control in the Clinical Laboratory--Increases in precision, accuracy, sensitivity, speed, reliability, and ease of analysis all serve to enhance the analytical utility of a determination. Of the many means used to effect these improvements, the most exciting to arise in the recent past has been the digital computer. However, until recently, the computer has been used mainly for bookkeeping and data reduction. Its major contribution to automated systems clearly lies in its ability to control the entire analytical process in a closed-loop system sense.

Miniaturization--The miniaturization of laboratory instruments for use in intensive care units, cardiac care units, operating rooms, outpatient departments and accident wards is gradually being accomplished. It is hoped that such miniaturization will help cut costs, improve quality, and increase access to medical care.

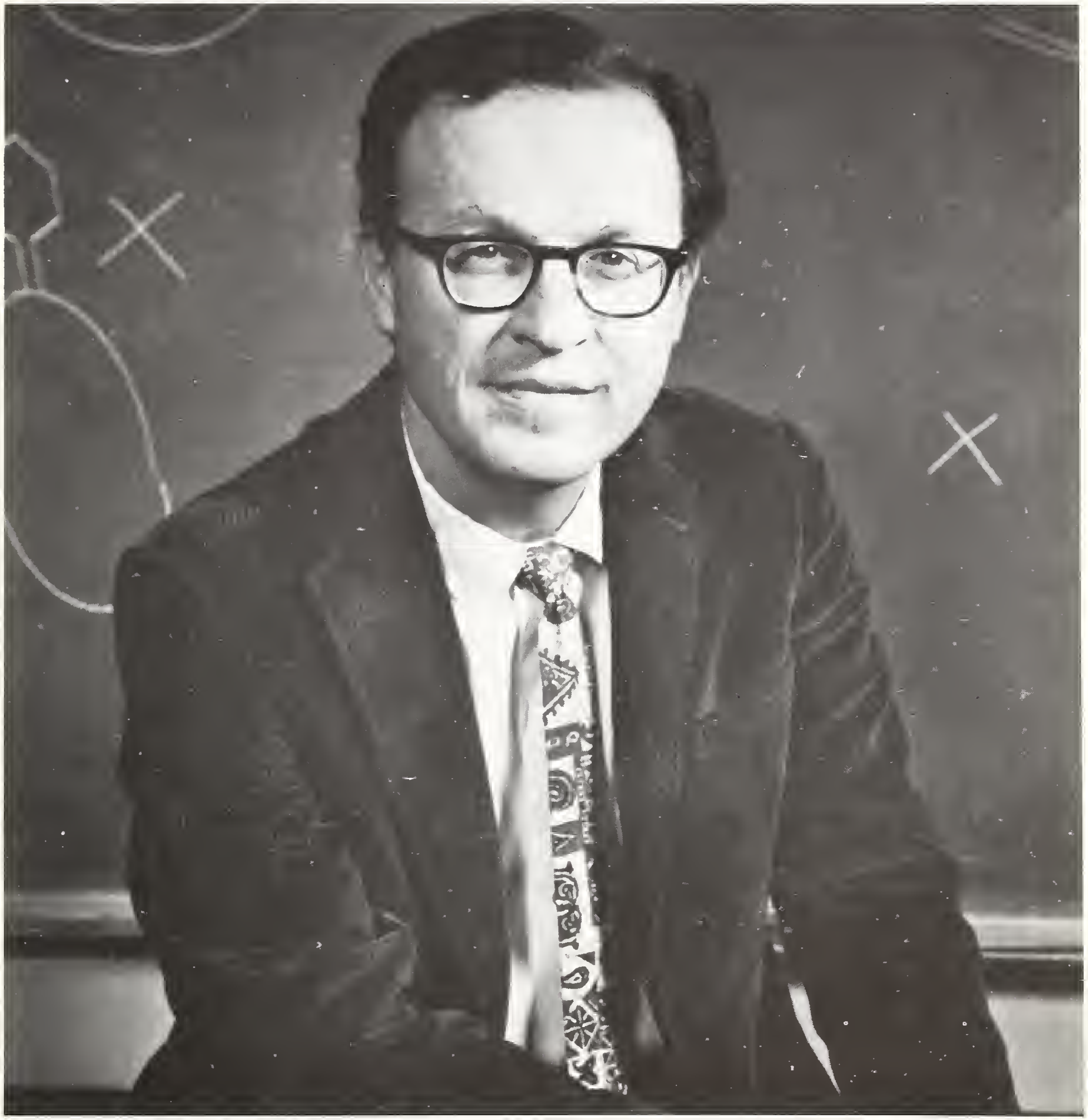
## INFORMATION EXCHANGE

In the interest of presenting new and advanced analytical concepts during their formative stages to as wide an audience of development and user personnel as possible, the Institute has organized a series of annual symposia on "Advanced Analytical Concepts for the Clinical Laboratory." The Seventh Annual Symposium on Advanced Analytical Concepts for the Clinical Laboratory was held at the Oak Ridge National Laboratory under the joint sponsorship of the Institute and the Atomic Energy Commission in March 1975.

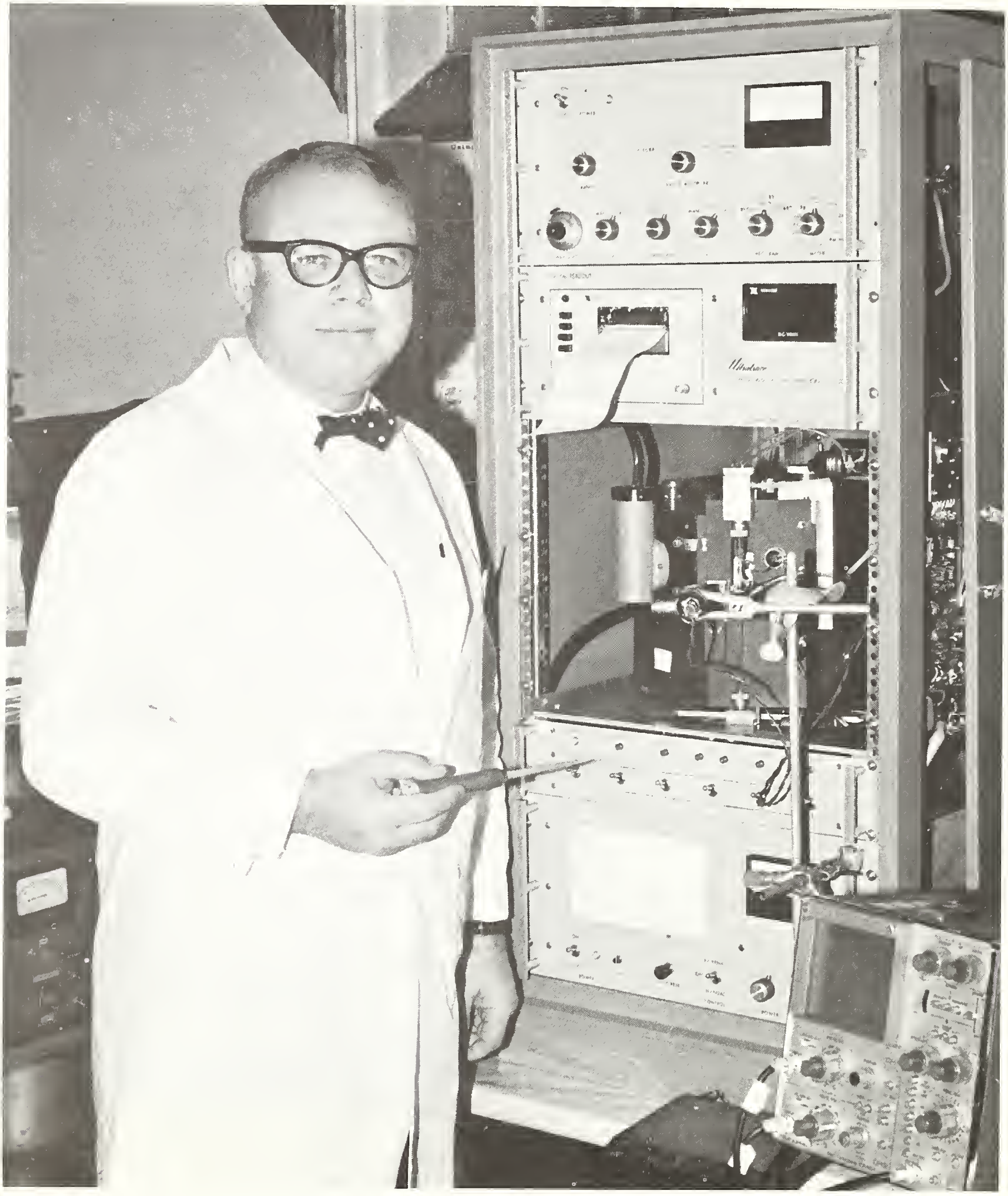


Dr. Melville

*This Introduction was prepared by Robert S. Melville, Ph.D., who is Chief, Automated Clinical Laboratory Section, Biomedical Engineering Program, National Institute of General Medical Sciences. For more information about the Program, please contact Dr. Melville or Mrs. Vivian Dobson, Program Assistant, at (301) 496-7081.*



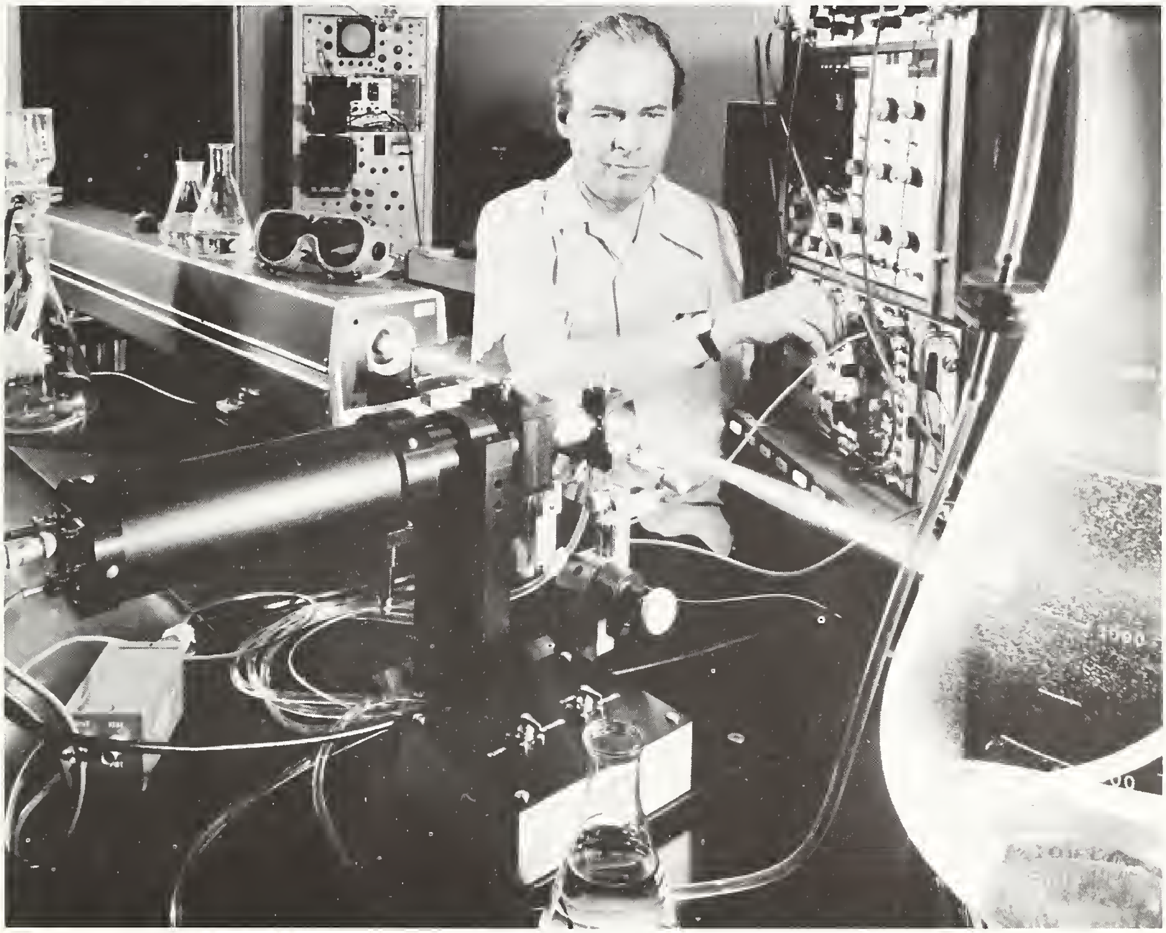
*BERKELEY, CA--Donald A. Glaser, Ph.D., a Nobel Laureate in physics, has recently completed the first totally-automated device for culturing and studying multiple colonies of bacteria. He is particularly interested in studies of genetic mutants. Today, Dr. Glaser can identify 10 rare mutants a week from hundreds of thousands of colonies. Using conventional methods, it is considered fortunate to obtain 10 mutants in a year. (NIH Photo #ACL-1)*



*BOSTON, MA--Bert L. Vallee, M.D., of the Biophysical Chemistry Laboratory, Peter Bent Brigham Hospital, pauses after injecting a sample of biological material into a microwave plasma emission detection unit which detects tiny amounts of metals. (NIH Photo #ACL-2)*

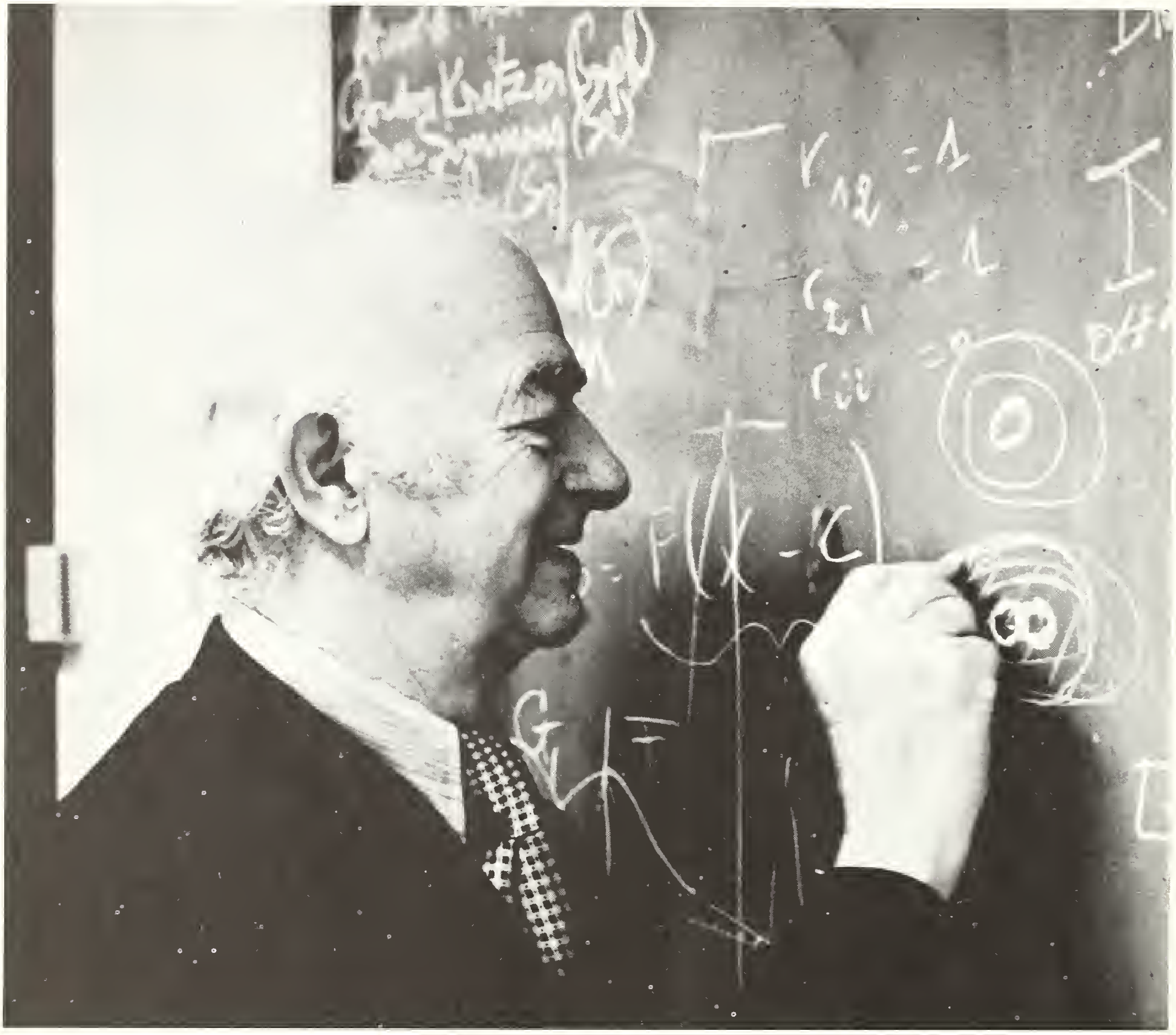
*BIRMINGHAM, AL--Seymour S. West, of the University of Alabama, is shown with his microspectrofluorophotometer by which various live cells or selected portions of a single cell can be studied. (NIH Photo #ACL-3)*

*CHARLOTTESVILLE, VA--Jesse Beams, Ph.D., of the University of Virginia, adjusts his ultra-sensitive magnetic suspension balance. This balance can detect weight differences of* $10^{-11}$ *grams of material. Such sensitivity is needed for measuring densities and partial specific volumes in biological fluids. (NIH Photo #ACL-4)*



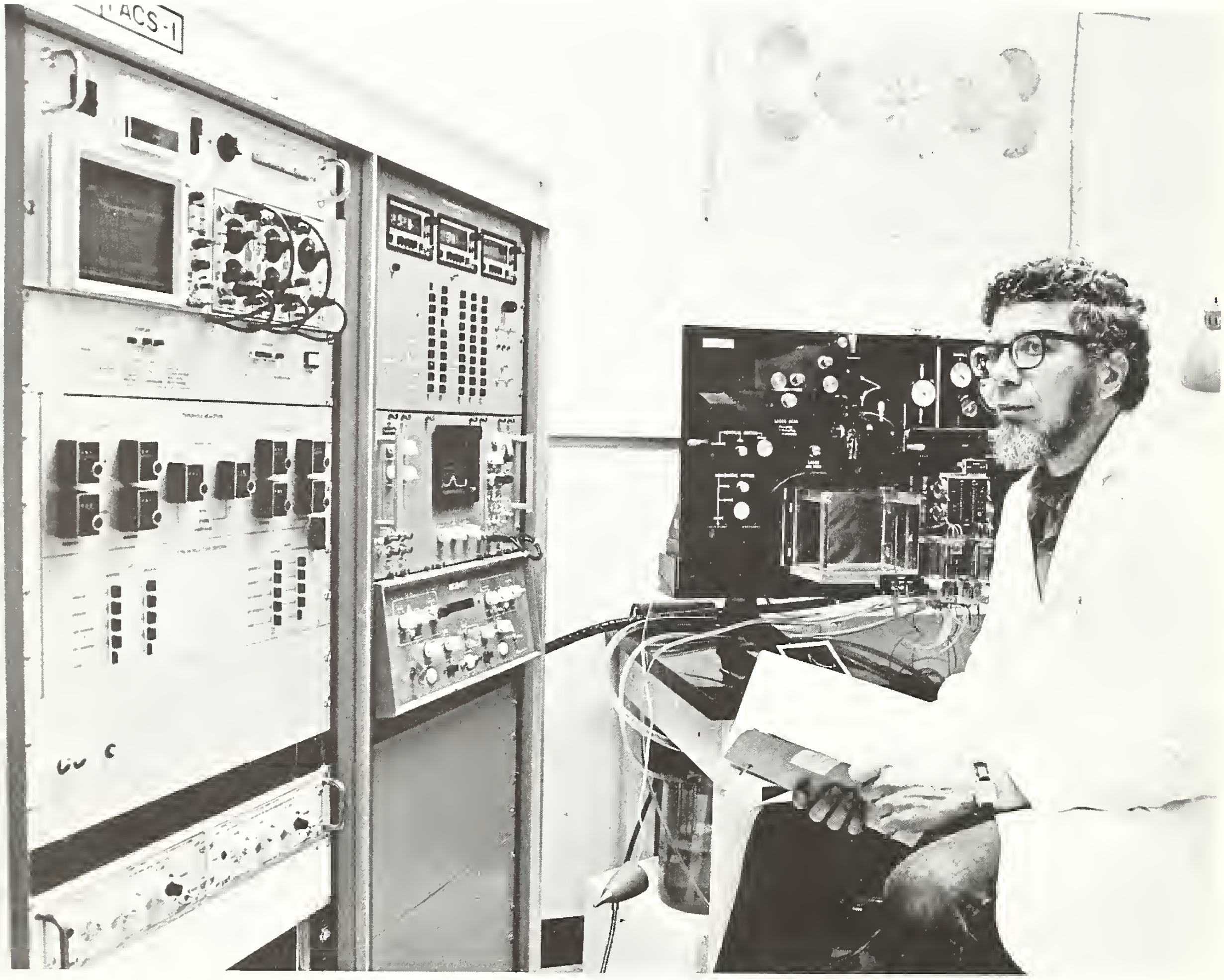
*LIVERMORE, CA--Marvin Van Dilla, Ph.D., of Lawrence Livermore Laboratories, is shown adjusting the Argon ion laser which is an integral part of the flow system around which his research centers. (NIH Photo #ACL-5)*

MENLO PARK



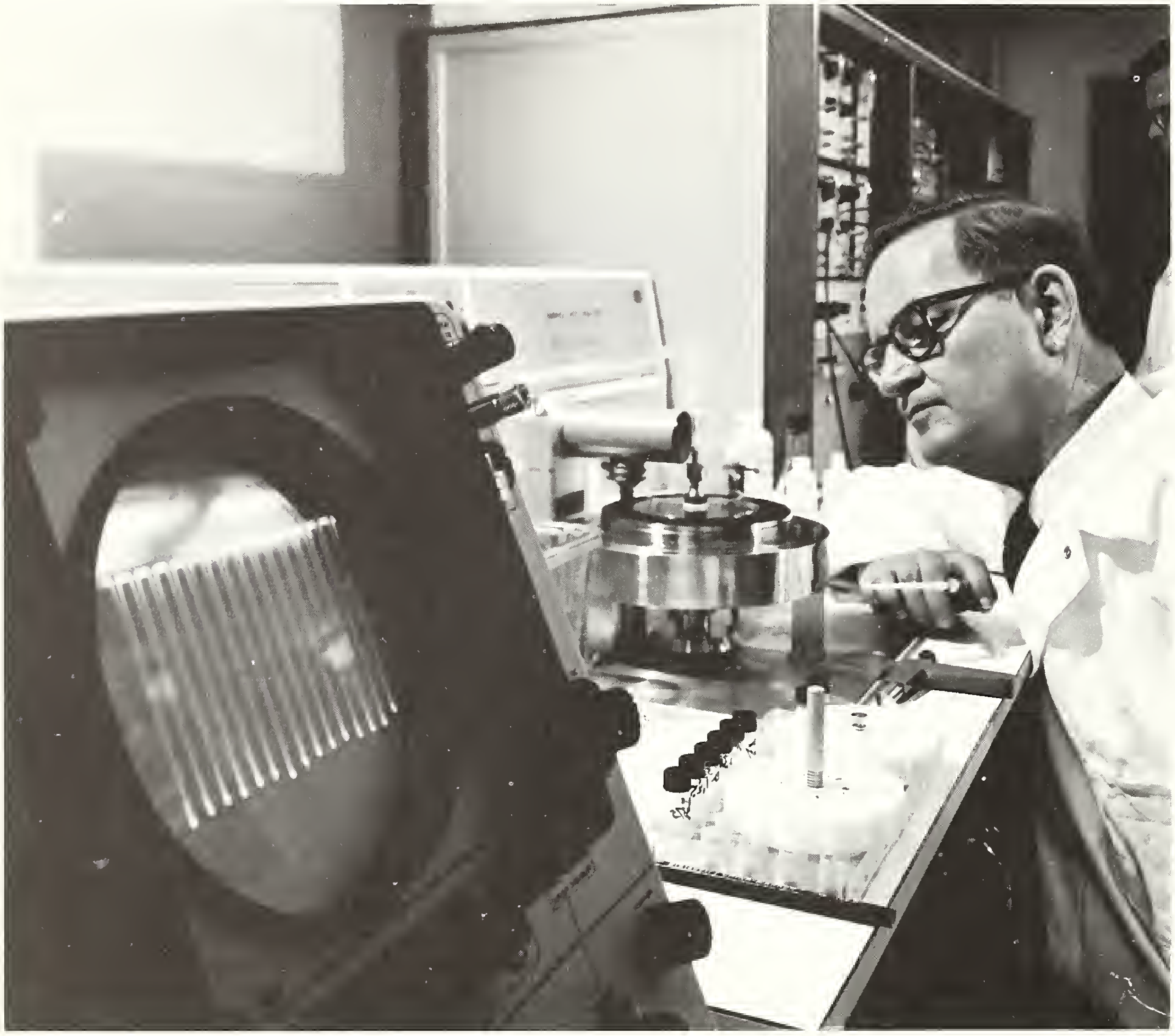
*MENLO PARK, CA--Linus Pauling, Ph.D., president of the Linus Pauling Institute of Science and Medicine, and twice Nobel Laureate, directs a project which has as its goal, the development of pattern-recognition programs which will allow discrimination between normal and diseased states on the basis of gas chromatographic and mass spectrometric profiles of human urine. (NIH Photo #ACL-6)*

*MADISON, WI--Stuart J. Updike, M.D., is developing a system of automation of radioimmunoassay. This NIGMS-funded project is based on a reusable, solid phase antibody binding reagent. Automation is achieved using a modified drill press, which allows 100 determinations at once. Pipetting and centrifugation steps have been eliminated. (NIH Photo #ACL-7)*

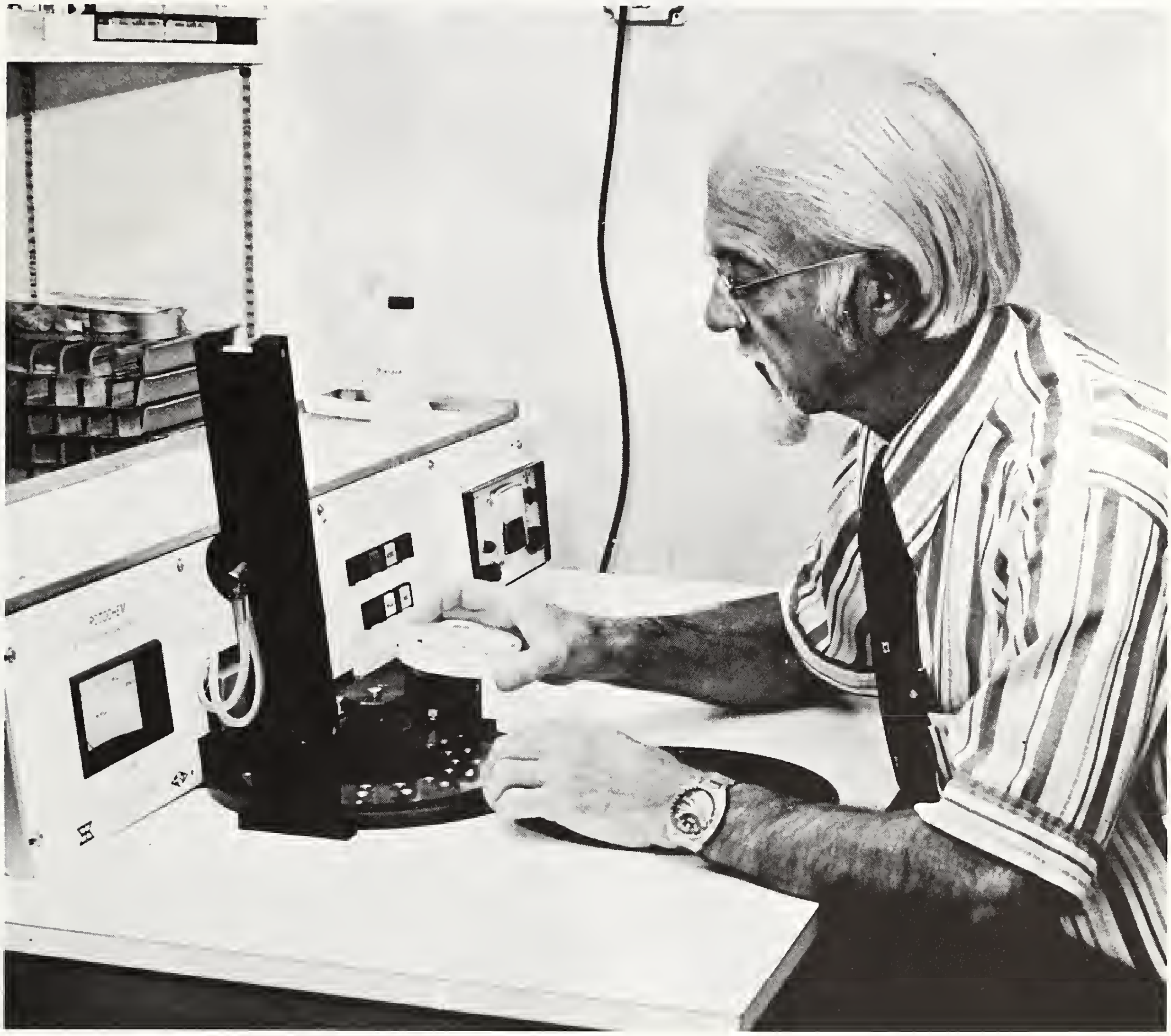


*STANFORD, CA--Leonard Herzenberg, Ph.D., headed a team of Stanford University Medical Center researchers that developed an instrument to separate human cells. The cell separator is now being produced commercially for use in many research laboratories. The first commercial version of the instrument (shown at left) is now in operation at Stanford. (NIH Photo #ACL-8)*

*WASHINGTON, DC--Martin Rubin, Ph.D., of Georgetown University Hospital, adjusts the visual display of an Electro Nucleonics GEMSAEC in his clinical chemistry laboratory. (NIH Photo #ACL-9)*



*OAK RIDGE, TN--Norman G. Anderson, Ph.D., inventor of the fast clinical analyzer commonly known to scientists as GeMSAEC, studies the action of reagents immediately following their injection into the original prototype. The instrument has great potential for application in large and small clinical laboratories throughout the United States. The acronym GeMSAEC reflects the cooperative efforts of funding between the National Institute of General Medical Sciences and the Atomic Energy Commission. (NIH Photo #ACL-10)*



*SAN FRANCISCO, CA--George Z. Williams, M.D., director of the Institute of Health Research of the Institutes of Medical Sciences, loads a Roto-Chem, one of the three original commercial prototypes of the GeMSAEC. The instrument performs rapid, accurate chemistry determinations on human biological fluids. (NIH Photo #ACL-11)*

*URBANA, IL--Howard V. Malmstadt, Ph.D., of the University of Illinois, inspects a rotor from the prototype mini-GeMSAEC. He is working closely with scientists from the Oak Ridge (Tennessee) National Laboratory in performance evaluation of the instrument. (NIH Photo #ACL-12)*

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NIH News Branch
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Phone: (301) 496-1206

Research Advances

# NIH STUDIES NERVE IMPULSES INVOLVED IN VISION PROCESS

Studies by scientists of the National Heart and Lung Institute (NHLI) and the National Eye Institute (NEI) suggest that guanosine triphosphate (GTP) and a cyclic meleotide made from GTP called cyclic 3'-5' guanosine monophosphate (cyclic GMP) may participate in the complex sequence of events by which light, falling on the retina of the eye, generates the nerve impulses involved in vision.

The scientists are Gopal Krishna, Ph.D., and N. Krishnan, Ph.D., of NHLI, and R. Fletcher, P.O. O'Brien, Ph.D., and G. Chader, Ph.D., of NEI. They reported their findings to the April 1975 Annual Meeting of the Federation of American Societies for Experimental Biology.

The retina contains two types of photoreceptor cells: rods and cones. Rods permit vision in dim light, but yield poorly defined images and cannot discern color. Cones function in bright light, enable perception of clear, sharp images, and are responsible for color vision.

The light-sensitive unit of each rod is the outer segment. This segment consists of hundreds of closely packed, parallel discs composed mainly of the visual protein rhodopsin. The "business end," or prosthetic group, of the rhodopsin molecule is vitamin A (also called retinal).

Light energy striking the rods of the retina is absorbed by rhodopsin, producing a change in the conformation of its vitamin A prosthetic group. Subsequently, the vitamin A passes through several intermediate stages and then is split off from the protein portion of the rhodopsin molecule. In the course of these events, the absorbed light energy is converted into an

(more)

electrical impulse that travels to the brain via the optic nerve. Finally, rhodopsin is regenerated by recombination of the protein with vitamin A.

The NHLI and NEI scientists found that the rhodopsin-rich discs of the outer segment of rod cells contained very high concentrations of cyclic-GMP--indeed, much higher concentrations than are found in any other tissue of the body. The outer segment also contained a highly specialized enzyme system for the generation of this compound (from GTP) and for its degradation. The high activity of this enzyme system suggested a rapid rate of turnover for cyclic-GMP in the outer segment.

These observations raise the possibility that GTP and cyclic-GMP may well be involved in the visual process, perhaps as participants in the energy-conversion reactions by which light is converted into electrochemical energy for propagation as nerve impulses and perhaps in the regeneration of rhodopsin.

There are several intriguing parallels between the GTP-cyclic-GMP system and the more intensively studied ATP-cyclic-AMP system found in other tissues. In the latter system, ATP (adenosine triphosphate), the immediate source of energy for most of the energy-consuming processes of metabolism, can also be converted into cyclic-AMP by an enzyme called adenylate cyclase. In turn, cyclic-AMP appears to be a key "second messenger" substance through which various hormones or other regulatory stimuli enforce their directive on target tissues. According to this "second messenger" hypothesis, the chief action of a hormone on susceptible tissues is to stimulate the activity of their adenylic cyclase, thus increasing the rate of cyclic-AMP formation in these

(more)

tissues. The cyclic-AMP mediates the hormonal effects and then, its job done, is inactivated by another enzyme called a phosphodiesterase. Similarly, cyclic-GMP is generated from GTP by the enzyme guanylate cyclase and inactivated by its own phosphodiesterase in the photoreceptor cell. These observations suggest that cyclic-GMP may be involved in the mediation of the neural response of the retina to light.

The presence in the retinal rods of high concentrations of cyclic-GMP together with the enzymes involved in its production and degradation similarly suggests that the GTP-cyclic-GMP system is probably involved in the response of the retina to light. Exposure of the rods to light sets many reactions in motion, including the breakdown of cyclic-GMP by its phosphodiesterase (provided that GTP or ATP is also present). The increased turnover of these compounds suggest participation in reactions of the visual cycle, though their precise role, if any, remains to be defined.

As described earlier, the rhodopsin molecule splits into its protein component (called opsin) and vitamin A after exposure to light. In their studies the NHLI and NEI scientists found the discs of the outer segment of the retina contain a protein kinase that phosphorylates opsin, preferentially using GTP as the phosphate donor. The scientists also found that phosphorylated opsin was converted to rhodopsin by treatment with vitamin A (11-cis retinal).

The GTP-opsin kinase was activated by light and inhibited by calcium, which has been shown to mimic the electrophysiological effects of light on the photoreceptors of the retina. The activity of the GTP-opsin kinase also

(more)

appeared to be subject to the control of cyclic-AMP. The GTP-opsin kinase was completely inhibited by phosphate. But phosphate activates another protein kinase that also phosphorylates opsin, using ATP as the phosphate donor. This suggests the presence in the rods of two systems, possibly complementary, for carrying out the phosphorylation step that may precede the regeneration of rhodopsin. For though the role of opsin phosphorylation in the visual cycle is not clearly understood, changes in the rate of phosphorylation occur in photoreceptor cells of the retina within one second after exposure to light. These changes may be indicative of the regeneration of rhodopsin molecules that have been broken down by the same stimulus.

#

**NEI PRESS BRIEFING**--The National Eye Institute (NEI) will host its first press briefing on Thursday, June 12, at 10 a.m., as one in the series of NIH Science Writers Seminars. The briefing at NIH will serve as a report on the five-year-old Institute's growth and development, and will provide a forum for discussion of the most significant advances in vision research. For more details, contact Julian M. Morris or Ms. Bonnie F. Spellane at (301) 496-5248.

#

**COLITIS**--Ulcerative colitis is a progressive, inflammatory disease of the colon, or large bowel. Affected persons may suffer from cramps, repeated bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals, according to the National Institutes of Health.

#

Research Advances

## TOTAL BODY IRRADIATION DOUBLES AVERAGE LEUKEMIA SURVIVAL TIME

Treatment with total body irradiation has doubled the average survival time for cancer patients with chronic lymphocytic leukemia (CLL), according to Ralph E. Johnson, M.D., chief of the National Cancer Institute's (NCI) Radiation Oncology Branch.

"This is the first time remissions have been achieved of sufficient degree to alter the natural history of the disease in a significant number of patients," Dr. Johnson told attendees at the annual meeting of the American Association for Cancer Research, held in May 1975.

In the 10-year NCI study, one-third of a group of 48 patients who received total body irradiation for untreated, progressive CLL experienced a complete disappearance of all clinical symptoms of the disease. The median survival time (the time at which half of the patients remained alive) for the 48 patients was 57 months from the time of first treatment. Two patients were alive and free of disease after 10 years.

Another group of 18 patients with progressive CLL was treated with local irradiation and anticancer drugs. The median survival time for patients in this group was only 27 months.

Chronic lymphocytic leukemia is diagnosed in about 5,500 persons a year in the U.S. Previous studies reporting treatment of the disease by various methods have indicated that only partial and temporary remission of the disease could be obtained, Dr. Johnson said.

As in the earlier studies, the disease status in the NCI study was not improved in patients receiving local irradiation and chemotherapy. However,

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patients who did not show a complete response to total body irradiation also had no improvement in other disease parameters.

"Only in patients with a complete remission has a change in disease status been observed," the NCI scientist said.

Patients who achieved a complete disappearance of CLL had improved immune responses, including recovery of normal immunoglobulin levels and resistance to infectious complications that are a serious problem with CLL patients. Patients were able to return to work and resume other normal activities.

The total body irradiation therapy involved dosages of either five rads per day five times a week or ten rads per day three times a week. A rad is a standard unit measuring radiation dosage. Half of the 48 patients received a total of 200-400 rads during the study. The other half received 100-200 rads. The differing dosages had no apparent effect on remission rates or survival times. The total dosages are only one-tenth of radiation dosages conventionally used in therapy of other forms of cancer, Dr. Johnson noted.

The NCI scientist expressed the hope that the results of the study would provoke a more optimistic attitude toward therapy of patients with chronic lymphocytic leukemia.

#

TISSUE GROWING--National Institutes of Health scientists have devised an artificial circulatory network that allows them to grow living animal cells in the laboratory to a density that resembles natural body tissue.

#

## Research Advances

### NCI STUDIES SUSCEPTIBILITY OF LEUKEMIA CELLS TO SOME DRUGS

Leukemia cells may be more susceptible to certain anticancer drugs than normal white cells because of a lower concentration of a regulatory biochemical (cyclic 3'-5'-adenosine monophosphate or cyclic AMP), according to Anthony W. Schrecker, Ph.D., a National Cancer Institute (NCI) scientist.

Drugs might become even more effective if a means could be found to reduce further cyclic AMP levels in leukemia cells, he suggested.

Dr. Schrecker presented his findings May 9, 1975, at the annual meeting of the American Association for Cancer Research, San Diego. The studies were conducted at the Scripps Clinic and Research Foundation, La Jolla, while the NCI investigator was there on sabbatical leave.

Scientists have suggested that cyclic AMP may be important in regulating growth of cells, Dr. Schrecker said. In laboratory studies, investigators have found that cancer cells may have abnormally low levels of the cyclic nucleotide.

The control of cell growth by cyclic AMP may be related to its effect on the uptake of nutrients by the cells. According to this theory, cancer cells grow without control because their lower intracellular level of cyclic AMP causes nutrients to enter more easily.

Because certain anticancer drugs mimic nutrients in their structure, the cancer cell may also incorporate these more easily than do normal cells, Dr. Schrecker postulated. One such anticancer drug is methotrexate. The cell mistakes it for folic acid, a B vitamin. The result is blocking of an enzyme critical to the synthesis of biochemical precursors of DNA (deoxyribonucleic

(more)

acid), the genetic molecule in the nucleus of the cell that regulates cell division.

To test this postulate, Dr. Schrecker exposed cultures of mouse L1210 leukemia cells to various compounds that alter the cellular level of cyclic AMP. He then added methotrexate tagged with a radioactive label and measured the ability of the cells to incorporate the anticancer drug. The mouse cells are an experimental model for acute lymphocytic leukemia in children.

When substances that increase the cellular level of cyclic AMP were added to the mouse cells, they took up methotrexate at a slower rate. Addition of substances such as cyclic AMP, its dibutryl derivative, and other cyclic nucelotides such as cyclic GMP and its dibutryl derivative inhibited the initial rate of methotrexate uptake by as much as 80 percent. 1-Methyl-3-isobutylxanthine, a potent inhibitor of phosphodiesterase (an enzyme responsible for reducing cyclic AMP levels), also inhibited the rate of methotrexate uptake.

When substances that decrease the cellular level of cyclic AMP were added to the leukemia cells, they took up the anticancer drug at an increased rate. Imidazole, a stimulator of the enzyme phosphodiesterase, thus increased the rate of methotrexate uptake.

Addition of cyclic nucleotides to the leukemia cells also depressed the rate of uptake of 5-methyltetrahydrofolate, the main metabolite of folic acid in the circulation. However, the depressed rate with the natural compound was less than that observed with the anticancer drug that mimics this compound.

These experiments seem to show that uptake of methotrexate in certain

(more)

Leukemia Cells (Cont'd)

leukemia cells is regulated by cyclic AMP, Dr. Schrecker said. If cancer cells indeed have lower levels of cyclic AMP, as suggested by the work of other scientists, then this could explain why they are more susceptible to the toxic effect of methotrexate than normal cells, he concluded.

#

**ALLERGIES**--The allergic reaction was recognized around 1900, but for many years little progress was made in understanding this complex phenomenon. More recent research has been fruitful, however, and the National Institute of Allergy and Infectious Diseases in 1971 established the first of what are now 17 Asthma and Allergic Disease Centers. In these Centers (including one on the NIH campus) physicians treat and study patients whose allergic problems may be benefitted by findings obtained from fundamental studies in immunology. Selected patients include those with asthma (particularly children), allergic rhinitis or hay fever, contact dermatitis, and allergic reactions to insect stings, drugs, chemicals, pollen, and foods.

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Research Advances

Background Report...

## CANCER DRUG TREATMENTS MAY INCREASE SECOND CANCER RISK

Although drug therapy is unquestionably useful in tumor control, a National Cancer Institute (NCI) scientist has reported that some patients treated successfully with certain anticancer drugs may have an increased risk of developing a second cancer.

Susan M. Sieber, Ph.D., of the NCI Division of Cancer Treatment, based her report on documented cases that appeared in the medical literature of second cancers following chemotherapy for the original tumor. The data were presented to the annual meeting of the American Association for Cancer Research in May 1975.

Two forms of cancer and their respective drug therapies were found to be associated with a higher than normal incidence of acute myelogenous leukemia (AML):

* Hodgkin's disease treated with vincristine, nitrogen mustard, chlorambucil, or with combination chemotherapy (nitrogen mustard, vincristine, procarbazine and prednisone) plus irradiation.

* Multiple myeloma treated with Melphalan (phenylalanine mustard, L-PAM).

AML has developed at rates up to 100 times those expected in the general population in some groups of Hodgkin's disease patients, according to the NCI scientist. AML has developed at rates from 100 to 1,000 times those of the general population in some groups of patients with multiple myeloma.

The annual incidence of AML in the U.S. is estimated at 2.2 cases per 100,000 population.

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Seventeen of the 23 second cancers that occurred in Hodgkin's disease patients who had received drug therapy were acute leukemia, while 32 of the 33 second cancers in multiple myeloma patients who had received L-PAM were also acute leukemia.

Cancers have also been associated with drug treatment of non-cancerous diseases which are life threatening, said Dr. Sieber. Kidney transplant patients, for example, are given Imuran, a drug that suppresses the immune system, to prevent graft rejection. These patients developed cancer at a rate 35 times higher than normal. In contrast to the acute leukemias seen in cancer patients, lymphomas were the predominant type of cancer in immunosuppressed patients. One form of lymphoma in particular, reticulum cell sarcoma, was found with great frequency in these patients.

Laboratory studies of mice exposed to high doses of anticancer drugs indicate that many of these agents are carcinogenic, capable of causing tumors in animals. Procarbazine, one of the four drugs in the combination for Hodgkin's disease, has been found to be a very potent cancer-causing chemical. It can induce many different types of tumors in mice, rats, and even monkeys.

Just because a drug causes cancer in a laboratory animal does not necessarily mean that it can also cause leukemia in cancer patients, Dr. Sieber emphasized. She offered several reasons that make it difficult to extrapolate from these animals studies to humans.

Even before treatment, cancer patients may already be at a greater risk of developing a second cancer than is the population at large. In addition, acute leukemia may be part of the natural history of myeloma or Hodgkin's

(more)

disease--a possibility that is only now becoming evident because of the increases in patient survival due to improved treatments.

Without chemotherapy many of these cancer patients would have died of their disease. Therefore, the benefit of treatment greatly outweighs the risk of a second cancer, Dr. Sieber said. However, when such a risk accompanies treatment for a condition that is not a threat to life, then the problem of whether or not to treat becomes more complex.

Currently, Imuran is also being used to treat kidney diseases, she noted. Cytotoxic drugs such as Cytoxan are being used for rheumatoid arthritis, and methotrexate is used to treat psoriasis. Careful evaluation of the long-term effects of these agents is now underway in the laboratory. Physicians administering cytotoxic drugs must weigh their potential benefits against the possible hazards.

Richard H. Adamson was Dr. Sieber's associate in the NCI report.

#

**CHOLESTEROL**--Elevated blood levels of cholesterol and other fatty substances (collectively called lipids) are often strongly associated with increased risk of premature arteriosclerosis and coronary heart disease, according to the National Institutes of Health.

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Research Advances

## ANTIBIOTIC TAKEN AFTER INTERCOURSE PREVENTS RECURRENT BLADDER INFECTIONS

Recurrent bladder infections in some women can be prevented by self-administration of a single oral dose of an antibiotic immediately after sexual intercourse. A National Institute of Allergy and Infectious Diseases grantee scientist at Stanford University found that this regimen over a period of at least 19 months greatly reduced the incidence of infection in 14 patients under study.

Chronic or recurrent infections of the lower urinary tract are a common and perplexing problem for the physician and a frustrating experience for the patient. In some women, recurrence of infection can be clearly related to sexual intercourse, presumably because it provides a means of entry of bacteria from the urethra into the bladder. Although varied methods for solving this problem have been tried, they have generally met with little success. Consequently, some patients will sharply curtail their sexual activity, leading to marital tension.

To test the prophylactic effectiveness of a single dose of an antibiotic taken immediately after intercourse, Kenneth L. Vosti, M.D., selected 14 patients from a larger group that had been observed prospectively for years in a special clinic for patients with urinary tract infections. Study patients all had a history of recurrent infections related to sexual intercourse.

The 14 patients had been studied for a total of 705 months, prior to prophylaxis. During this time 90 infections had occurred. In contrast, only 19 infections were recorded during the 761 months of study of the effects

(more)

of prophylaxis on the 14 patients.

The antibiotics used in the study were nitrofurantoin, cephalexin, nalidixic acid, sulfonamide, and penicillin G. None of the patients had to discontinue treatment because of allergic reactions or drug intolerance. A major concern when an antibiotic is administered over a long period of time is the frequent emergence of drug-resistant strains of an organism. Dr. Vosti found in his study that, although organisms resistant to one antibiotic did occasionally appear, they remained sensitive to the other drugs available. This problem of drug resistance seemed, therefore, to be more than offset by the major benefits of a decrease in the frequency of infections.

In his present practice, Dr. Vosti recommends discontinuing use of an antibiotic after approximately one year. Patients who begin to have multiple recurrences of infections are instructed to again take the prophylactic dose following intercourse. The decision to withdraw medication is individualized, and is usually related to the inconvenience of recurrent infections to a patient in terms of psychologic stress or absence from work.

Dr. Vosti reported results of his study in the March 3, 1975,issue of the *Journal of the American Medical Association.*

#

ELECTRON MICROSCOPES--The invention and refinement of the electron microscope has been the most dramatic development in modern microscopy, according to the National Institutes of Health. The electron microscope has enabled scientists to delve further into the structure of cells.

#

Research Advances

Memory Formation...

## SCIENTISTS STUDY ROLE OF BRAIN CHEMISTRY IN LEARNING PROCESS

Results of recent research conducted at Northwestern University, Evanston, "are promising in linking the experience of learning and memory to brain chemistry."

So believes Aryeh Routtenberg, Ph.D., professor of Psychology and Biological Sciences and director of the Neuroscience Program at Northwestern, who supervised the research with the collaboration of Yigal H. Ehrlich, Ph.D., and Ronald R. Rabjohns.

"A change in brain chemistry is thought to be a crucial link in the formation of memories during learning," says Dr. Routtenberg. "The problem has been to show where this takes place in the brain, what part of the brain cell might show the change and what chemicals in that part of the brain cell will be changed."

Dr. Routtenberg's research shows that 24 hours after a brief learning experience, the chemical composition changed in particular proteins associated with the brain cell membrane in one particular brain region.

In the experiment, adult rats are trained to avoid a painful footshock by staying up on a platform for 10 minutes. After the training, the rats are returned to their cages for 24 hours.

"At that time, protein analysis is done on membrane preparations taken from several different brain regions," says Dr. Routtenberg. "One protein component, following separation of proteins by electrophoresis, showed a dramatic change in the group of rats that had learned." But no such dramatic

(more)

change was found in a test control group of handled rats or rats that received only shock.

Dr. Routtenberg cautions that "these results do not yet prove that there is a link between a particular protein molecule and memory formation," but "they do provide a reasonable basis for pursuing such a hypothesis."

This work is supported in part by the National Institute of Neurological and Communicative Disorders and Stroke. Findings were presented at the annual meeting of the Federation of American Societies for Experimental Biology in April 1975 in Atlantic City.

#

ANTIVIRAL AGENTS--Viral infections are the most common of those affecting the public and a number of drugs and other antiviral substances are under investigation by the National Institute of Allergy and Infectious Diseases for possible use in treatment. One of these substances, called interferon, is a protein produced by body cells in response to invasion by an infectious agent. Scientists are studying the effects of above-normal amounts of interferon on viral infections. They are also developing ways to produce interferon outside the body or to increase the body's production without toxic side effects.

#

Research Advances

# ENZYME RESEARCH YIELDS FACTS ABOUT SJOGREN'S SYNDROME

A study of the starch-digesting, amylase enzyme that originates in salivary glands, shows that victims of Sjögren's syndrome fall into two distinct classes, and suggests that such enzyme research may, in time, help clinicians to monitor and manage these patients better.

Robert O. Wolf, D.D.S., reported the findings of a group of scientists at the National Institute of Dental Research to delegates attending the 1975 General Session of the American Association for Dental Research on April 6, 1975 in New York. He said that although most of the amylase made in the salivary and pancreatic glands goes directly through ducts to digest starchy foods passing through the alimentary canal, some amylase is always present in serum. Modern techniques of acrylamide gel electrophoresis and the insoluble starch dye-release method enable him to distinguish, measure, and compare the amounts of both forms of the enzyme in blood under conditions of health and disease.

The investigators analyzed the blood of 29 patients, mostly females, aged 24 to 75 years who are known to have Sjögren's syndrome, as compared with blood from 12 non-afflicted women of similar ages. This disease is relatively uncommon, and usually affects women. It is diagnosed as such when three kinds of symptoms occur together: dry mouth from too little saliva; dry, inflamed eyes from too few tears; and rheumatoid arthritis or some other type of collagen disease.

All of these patients had normal levels of pancreatic amylase in their blood streams, and only a few had somewhat high levels of total amylase.

(more)

Sjogren's Syndrome (Cont'd)

However, the levels of salivary amylase fell into two very different groups. Five patients had three or four times as much salivary enzyme as the normal control group. In the other 22, salivary amylase was not significantly different from the norm statistically, although it averaged slightly higher than in the control group of women.

Dr. Wolf hopes that further research will show whether the differences in salivary amylase in blood reflect two different types of Sjögren's disease, or two stages of the same disease. Because prior research with cystic fibrosis patients and other people suffering from acute damage (such as trauma, infections, or radiation) to the pancreas has shown that the blood level of pancreatic amylase rises sharply after the trauma and returns to normal as the patient recovers, he thinks it is more likely that high levels of salivary amylase in serum occur during acute blockage of salivary ducts, and lower levels may develop later when chronic disease has presumably reduced the ability of the glands to make the enzyme.

#

SICKLE CELL--In the United States, sickle cell trait occurs in about two million black people. Sickle cell anemia, the severe form of the sickle cell problem, affects about 50,000 blacks, who may undergo painful episodes called sickle cell crises, reports the National Institutes of Health.

#

Research Advances

## NCI SCIENTISTS MAY HAVE FOUND ELUSIVE "STEM CELL"

Scientists at the National Cancer Institute (NCI) believe that they may have found the elusive "stem cell" from which all blood cells develop, according to Ronald D. Barr, M.D., of NCI's Division of Cancer Treatment. For more than 100 years, scientists have tried to isolate this precursor cell.

A lengthy process of separating the white blood cells taken from normal human donors into different types and subtypes allowed the scientists to isolate a fraction that differentiated into all other forms when later cultured. Preceding isolation of the stem cell fraction, the white blood cells were separated into their different component types by sedimentation procedures that layered cells by their differing densities and sizes.

Since the resulting separation was still incomplete, the fractions were then subjected to other techniques that divided the cells on the basis of their immunological properties.

Several different samples of leukocytes were thus obtained, only one of which was capable of differentiation.

When placed in tissue culture the reproducing stem cells multiplied into maturing red and white blood cells and blood platelets.

Jacqueline Whang-Peng, M.D., and Seymour M. Perry, M.D., were Dr. Barr's associates in the NCI investigation.

#

Research Advances

## S. MUTANS IDENTIFIED BY NEW COLOR METHOD

Investigators at Forsyth Dental Center, Boston, have developed a new color method for identifying colonies of all the varieties of *Streptococcus mutans* growing among other oral streptococci.

Oral bacteria are plated and incubated as usual on mitis salivarius agar which is selective for streptococci. Then the colonies are sprayed with a solution of mannitol, a substance which only *S. mutans* and some of the enterococci can ferment. After a brief second incubation period, the plates are sprayed with a fresh solution of a dye (2,3,5-triphenyl tetrazolium). Colonies of *S. mutans* turn pink and can easily be counted with the naked eye. All other colonies remain blue. Colonies of enterococci if present, can be distinguished from *S. mutans* because they stain bright red.

The new method should be useful not only for identifying *S. mutans* separately from other streptococci, but also for relating the numbers of these organisms to the total count of streptococci without the necessity of time-consuming inspection under a dissecting microscope.

Olga G. Gold, Harold V. Jordan, Ph.D., and Johannes van Houte, D.D.S., report these findings in the *Archives of Oral Biology*, March 1975.

Their research work is supported by a grant from the National Institute of Dental Research.

#

Research Advances

## DIET OF PREGNANT RATS MAY AFFECT EYES OF OFFSPRING

Researchers at Virginia Tech, Blacksburg, have shown that there may be a previously-unrecognized relationship between certain nutrients in a pregnant rat's diet and the development of congenital cataracts in her offspring.

In a research project sponsored by the National Eye Institute, George E. Bunce, Ph.D., and John L. Hess, Ph.D., worked on experiments involving the diets of pregnant and lactating rats.

They found that if they deprived the female rats of tocopherol (vitamin F) and tryptophan, one of the amino acids, that the combination of these two, resulted in a significantly higher incidence of cataracts in the progeny at weaning.

They presented the results of the work in a paper entitled "Cataracts in the Progeny of Rats Fed Diets Low in Tryptophan and Tocoherol During Gestation and Lactation," at the annual meeting of the Federation of American Societies for Experimental Biology in April, 1975.

The researchers reported that in the work they found that if they deprived the pregnant rats of only vitamin E, the progeny have about five percent or less incidence of cataracts. If they deprived the females of tryptophan, the progeny were apparently normal with regard to the lens of the eye.

"However, with the simultaneous restriction, the young have cataracts at weaning at a rate of five to six times normal so that the effect of simultaneous deprivation is more than just additive," Dr. Bunce said.

Drs. Bunce and Hess both cautioned that any significance for humans is conjectural at this time. "There is no reason, at this point, to think the combined deficiency has led to any case of congenital cataracts," they said.

#

Photo Feature

# SEARCH FOR NEW "BRACES" GIVES MONKEYS NEW FACES

The traditional practice of banding teeth to correct faulty bite may be replaced in part by the altering of facial bones, suggests research conducted at the University of Washington, Seattle, by Benjamin Moffett, Ph.D.

Dr. Moffett, professor of Orthodontics, is working with other professors and graduate students in testing new appliances for correcting dental malrelations, cleft palate, and other craniofacial conditions.

Their research, conducted on monkeys from the University's Regional Primate Research Center, involves the alteration of the skeletal and muscular pattern of the monkey's face. Applied to human beings, these procedures could result in tailoring facial skeletal patterns to fit existing dentition. This approach differs from the conventional view of orthodontic treatment which primarily attempts to harmonize the teeth to fit the face.

"The skull and jaw is a complex of joints, separated by bones," said Dr. Moffett. "By remodeling the joints around the bones, you can move the jaws in relation to the skull."

The basis of current orthodontic treatment, according to Dr. Moffett, is the ease with which the periodontal joints, which connect teeth roots to the surrounding bone, can be remodeled. The monkey experiments, however, show that the joints in the upper jaw can also be altered.

"Even though pressure still is applied to the teeth," said Dr. Moffett, "any orthodontic appliance which transmits force beyond the periodontal joints will produce similar remodeling activity in the facial and cranial structures."

(more)

Orthodontics (Cont'd)

A problem that has long plagued orthodontists is relapse, the drifting of straightened teeth after bands are removed. The research of several graduate students working under Dr. Moffett led to a simple surgical solution.

"Teeth are connected by bundles of collagen fibers that pass over the top of the bone," said Dr. Moffett. "The fibers connect one tooth to another and their natural tendency is to contract and keep pulling the teeth together."

When a tooth is moved by an orthodontic appliance, he explained, the fibers are moved, but they may go back to their former position when the bands are removed. With the new procedure, the orthodontist or dentist merely interrupts these fibers with a small incision after the orthodontic treatment is completed. As new fibers grow in, they reattach in the proper direction.

"Our graduate students showed the operation was successful on monkeys," said Dr. Moffett, "and it has been performed in University of Washington clinics for the last five years."

Monkeys are used for dental research because their dentition and jaw growth patterns are similar to those in humans. These processes occur at nearly three times the rate for humans, speeding up research results. Finding the ideal animal model is not easy, however, since monkeys usually do not have dental malocclusion.

Dr. Moffett's research work is supported by a grant from the National Institute of Dental Research.

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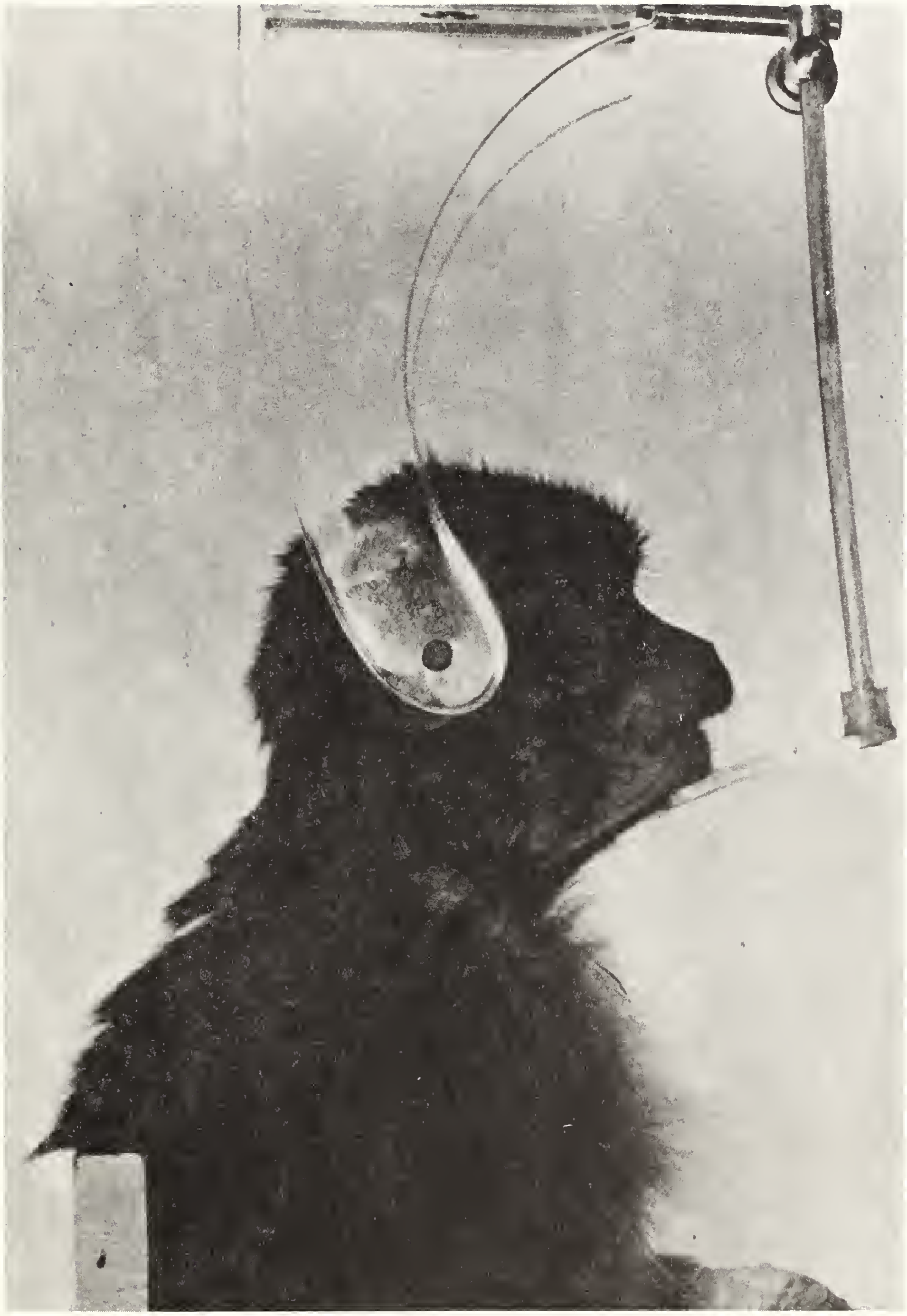
Orthodontics (Cont'd)



*This monkey's jaw has been realigned as part of an orthodontic study at the University of Washington. The study seeks new ways of aligning teeth by altering the structure of facial bones. (NIH Photo #1393)*

#

Photo Feature

# HEART SURGERY ON INFANTS USES HYPOTHERMIA METHOD

Open heart surgery can be performed on infants as young as three months old through the use of hypothermia, a technique involving temporary stoppage of the heartbeat.

David H. Dillard, M.D., professor of Surgery at the University of Washington, headed a team in 1965 that performed open heart surgery using surface-induced deep hypothermia. In hypothermia, a state of low body temperature is induced by placing the child in a cooling tank. This decreases the metabolism rate and thereby the need for oxygen, permitting stoppage of the heartbeat.

The technique is used for infants too young or delicate to tolerate a heart-lung machine. The subjects have ranged from three to 22 months of age, and have weighed between 2.9 and 10 kilograms. Forty-four percent of the infants have weighed less than four kilograms.

Ether is used to anesthetize the baby preceding hypothermia. The patient is then placed on a plastic sheet and lowered into a cooling tank to float on ice water. Monitors are attached for electrocardiogram readings. As the body temperature drops, bags of crushed ice are packed around the baby to lower the temperature still further.

When the rectal temperature is down to 23 - 21° Centigrade (about 73° to 70° F.) the patient is elevated from the tank and prepared for the first incision. As the temperature drops to about 20 - 17° C. (68 - 63° F.), about 4 cc of Young's solution is injected into the aortic root to stop the heartbeat.

(more)

The operation is then performed in a dry, quiet field. The operating time available under hypothermia is 60 minutes, although Dr. Dillard said that most operations are performed in less than 40 minutes.

After the operation, the infant is immersed in a warm-water bath. A gentle massage restores the heartbeat. The chest incision remains open until the temperature reaches 30° C. (86° F.) to allow the surgeons to control possible bleeding.

Infants spend between one and three days in the intensive care unit after surgery. After about a day, they are able to take liquids normally.

Dr. Dillard said that patients generally have minimal complications and only rare bleeding. There has been no evidence, he said, of any neurological damage from the hypothermia procedure.

The type of hypothermia used at the University of Washington, Seattle, hospital is an adaptation of a method developed at the University of Sendai in Japan. Hitoshi Mohri, M.D., a pioneer in the development of the Japanese technique, was assisted in the modification by Dr. Dillard and others.

"A number of children who would have been lost because there was nothing that could be done," said Dr. Dillard, "can now be saved and, in effect, totally corrected during the first year of life with open heart surgery using hypothermia."

The research work of Dr. Dillard is supported by a grant from the National Heart and Lung Institute.

(more)

Hypothermia (Cont'd)

*An infant undergoing open heart surgery involving hypothermia is lowered into a cooling tank that is packed with bags of crushed ice. Monitors follow electrocardiogram readings, temperature changes, and arterial and venous pressure readings. In lower photo, the baby's heartbeat is being restored through gentle massage. The research is funded by the National Heart and Lung Institute. (NIH Photos #1394 and #1395)*

## Note to Subscribers

Ms. Jeannette Belliveau, an NIH summer journalism intern who is a student at the University of Maryland, prepared this story and assisted in the preparation of other stories in this issue.

#

Photo Feature

# COUNSELING CLINICS HELP AVERT GENETIC DISORDERS

The possibility of having a child with a genetic disorder, which occurs in about one out of 20 live births, may be reduced for high-risk couples by genetic counseling clinics that offer information, advice, and often reassurance.

At the Genetic Counseling Clinic of Stanford University Medical Center, diagnosis is performed using tests such as amniocentesis, which can detect almost 30 genetic diseases before a child is born. A sample is taken of the amniotic fluid surrounding the fetus, which contains fetal cells that have sloughed off. Cells are cultured in the laboratory so that the presence of biochemical and chromosomal defects can be detected.

Howard Cann, M.D., director of the clinic, suggests that pregnant women over 35 years old consider undergoing amniocentesis to determine if their baby might have Down's syndrome, or mongolism. The risk of having a child with this disorder is about 10 times greater for the mother 40 years of age than for the 20-year-old mother.

Other frequently occurring genetic defects are cystic fibrosis, sickle cell anemia, Tay-Sachs disease, and thalassemia.

"Couples should understand what the risk of complication is," said Dr. Cann. "It's actually very low for this test--fewer than one amniocentesis in 200 will develop complications."

In the majority of tests, the fetus can be shown to be free of the specific genetic disease, and the fears and anxieties of prospective parents can be allayed. However, should the result of the test indicate the child

(more)

will be defective, many couples consider abortion.

Genetic counseling is recommended for families with a known genetic defect, or when more than one family member is affected with the same abnormality. Other indications are two or more fetal losses, and sterility not due to physical factors.

Each couple at the Stanford clinic is counseled by a physician and a pediatric social worker. This counseling team outlines the risks of having a defective child, based on the completion of a comprehensive family tree, which is critical in determining genetic faults.

The counselors describe the "recurrent risk," or probability that the couple will have a genetically defective child. They also explain what the life of a defective child and his parents might be like: how long the child might live, and what the financial and emotional costs would be to parents, child, and society.

Dr. Cann discussed the effects of drugs and radiation on genes.

"There is controversy over whether pot and some other street drugs cause deformed babies," he said. "We have no convincing evidence that they do.

"We tend to be reassuring to women who have been exposed to X-rays before conception or during pregnancy," he added. "The levels of exposure are almost always low. There is little evidence that the usual amounts of radiation used in diagnosis injure the fetus."

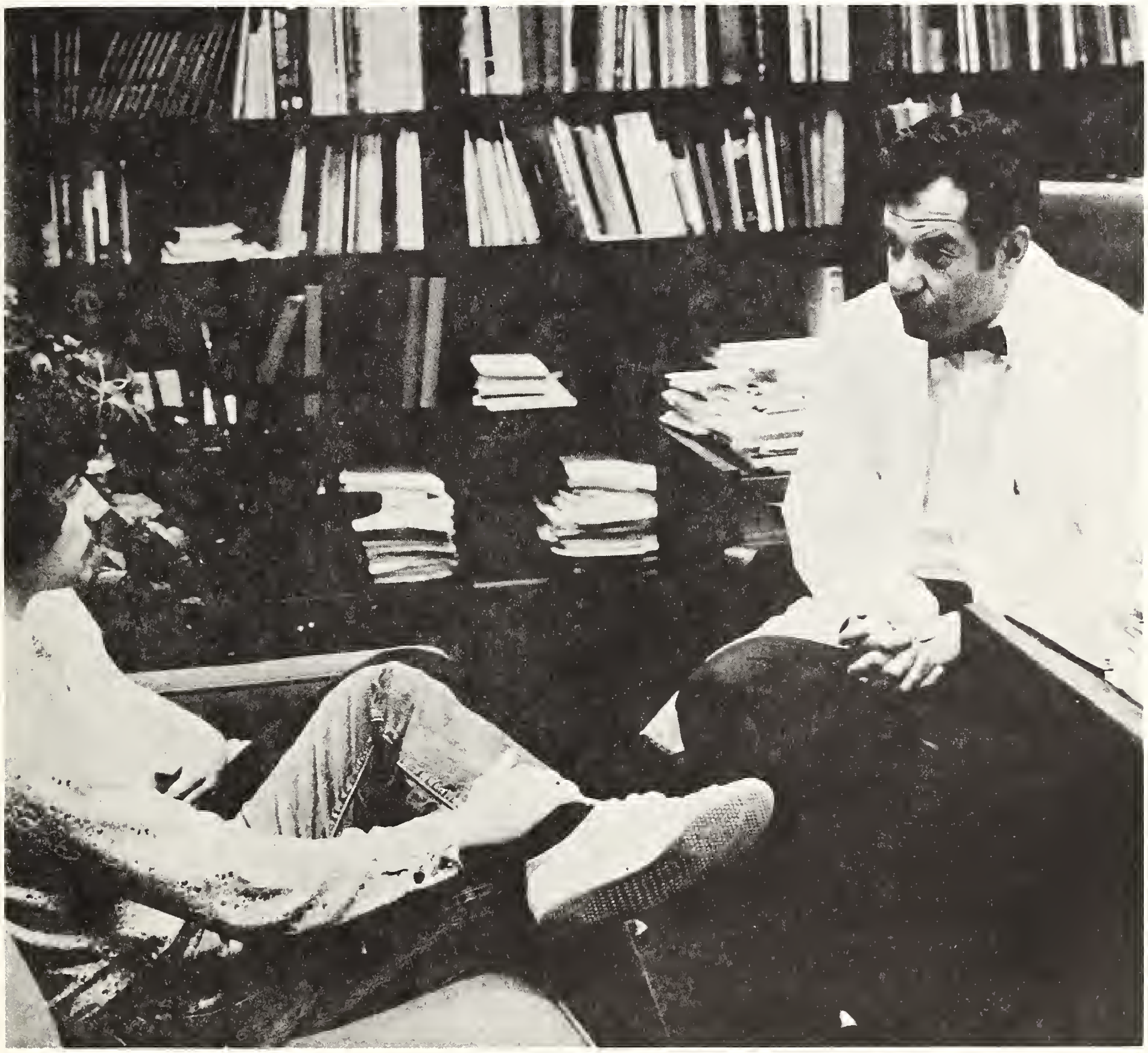
The burgeoning interest in genetic counseling has led to a proliferation of counseling clinics, university study programs, and medical genetics courses at medical schools.

(more)

Clinics (Cont'd)

"There is great interest in genetic disease now," said Dr. Cann, "because so much more progress has been made toward understanding it."

Dr. Cann's work is funded in part by the National Heart and Lung Institute.



*Some couples who have or suspect they may have a defective child come to the Genetic Counseling Clinic for help. The Clinic, which is at Stanford University Medical Center, is directed by Howard Cann, M.D. (right). (NIH Photo #1396)*

#

News Feature

# BIRTH DEFECT-CAUSING VIRUS LINKED WITH MOTHER'S IMMUNE DEFICIENCY

A common virus which causes severe birth defects in some infants has been linked with a specific immune deficiency in their mothers, according to a recent Georgetown University study.

Mothers of infants congenitally infected with cytomegalovirus (CMV) were found to have low cell-mediated immunity to the virus months after the birth of their defective children. Cell-mediated immunity is an important part of the body's defense mechanism which fights foreign invaders like viruses.

"This finding may open new doors in understanding the mysterious virus," according to Marek Rola-Pleszczynski, M.D., of the Department of Pediatrics. "Many women get CMV during pregnancy but not all of their children are affected. The mystery has been, why does this happen to some children and not to others?

"We hope that this discovery of a different and impaired immune response in mothers of afflicted children will ultimately lead to better methods of predicting CMV infection and a means of strengthening immunity in susceptible mothers to prevent birth defects in their children."

The most devastating form of CMV, he explains, is the infection in pregnant women which can cause spontaneous abortion, stillbirth, congenital deformities, retardation,and varying degrees of hearing, seeing and learning disabilities. Possibly as many as one in 1,000 babies suffer major or minor defects from the virus.

(more)

Immunity was studied, supported by the National Institute of Neurological and Communicative Disorders and Stroke, in 17 women with no history of abnormal births (the control group), and six mothers of babies suffering defects from CMV. They were tested for immune responses to CMV and to rubella virus, the latter also posing a threat of birth defects but which now can be prevented by vaccine. Both groups of mothers showed normal responses to rubella, indicating there was no general immune deficiency in the mothers of the affected infants. But the groups differed in antibody and cell-mediated immune responses to CMV.

The immune system recognizes and attacks foreign invaders through these two mechanisms which must "turn on": (1) antibodies (substances which destroy a virus by neutralizing or combining with it), and (2) cell-mediated responses (the action of white blood cells--lymphocytes--working to kill infected cells).

The major role of the latter mechanism has only recently been recognized in the rejection of organ transplants, and in the defense against viruses and certain forms of cancer, and possibly in production of chronic diseases like multiple sclerosis.

Results of the study showed:

- All affected infants excreted CMV in their urine; none of the normal children did.
- All the mothers of the affected infants and 10 of the 17 women in the control group had antibody evidence of previous CMV infection.

(more)

- Antibody response to CMV in the former group was higher than normal, indicating that the presence of the virus had stimulated antibody production, but had not provided protection against it.
- Cell-mediated immunity to CMV was low in all mothers of the affected babies, compared to the control group.
- Two women, never pregnant, who had persistent CMV were also studied and were found to have low cell-mediated immunity to CMV.

"The study seems to indicate," says Dr. Rola-Pleszczynski, "that there is a relationship between giving birth to a CMV-infected child and a specific immune deficiency in the mother."

A technique developed at Georgetown University was used to measure the function of the women's lymphocytes against rubella and CMV viruses. Non-infected cells and cells chronically infected with virus were tagged with the radioisotope Chromium$^{51}$. Lymphocytes from the two groups of mothers were added separately to these groups of target cells and their interactions studied. Measurement of the amount of chromium released when the lymphocytes destroyed or injured the infected host cells was interpreted as a measure of their reaction to virus.

#

DENTAL PLAQUE--Dental plaque is a colorless, transparent film on the teeth made up of saliva and bacteria materials. The National Institutes of Health reports that plaque contributes to tooth decay, and is also an agent in the cause and development of periodontal disease.

#

News Feature

# NEARLY 90 PERCENT OF NEWBORNS WITH RESPIRATORY DISTRESS CAN SURVIVE

Continuous positive airway pressure (CPAP) as a treatment for respiratory distress in newborn children now yields survival rates in the range of 90 percent. This amounts to a clear therapeutic breakthrough against this leading cause of neonatal death.

In about one percent of all newborn babies, life is immediately threatened because their lungs are immature and unable to retain the first breath of air. The first breath taken by all babies requires a great struggle, calling for 10 or 15 times the pressure needed to continue breathing once the lungs have been normally inflated. But immature lungs cannot retain the air; their air spaces collapse when the first breath is exhaled, and each succeeding inhalation is a struggle like the first. As areas of persistent lung collapse, or atelectasis, begin to spread and the infant's exhaustion and asphyxiation increase, plasma may ooze out into the repeatedly collapsing airways and form the glistening lining which formerly prompted physicians to name the syndrome "hyaline membrane disease." Now regarded as a condition of lung immaturity and largely an affliction of the prematurely born, the respiratory distress syndrome affects about 40,000 newborns in the U.S. each year and, until recently, killed more than half of these.

The idea of keeping the airways of these infants under continuous positive pressure originated with George A. Gregory, M.D., and his associates at the University of California School of Medicine in San Francisco. CPAP therapy was conceived as a way of overcoming an abnormally high surface tension in the lungs. Evidence had long been accumulating that the lungs of

(more)

infants with hyaline membrane disease are deficient in a complex surface-active substance that normally lines the air spaces at birth and regulates their surface tension during the breathing cycle. As inhalation enlarges the area of lung surface in contact with the air, elastic properties in this "surfactant" coating the airways come progressively into play, increasing airway surface tension and enhancing the lung's elastic recoil for the next, expiratory phase of the cycle. Then, as expiration rapidly shrinks the lung surface area, the surfactant sharply reduces the amount of surface tension that must be overcome to start the next inhalation. Without the surfactant to stabilize them, the immature lungs are forced to collapse on each expiration by the high surface tension.

"We thought that the application of a continuous airway pressure sufficient to balance the high surface tension might overcome the atelectasis and improve the arterial oxygenation," Dr. Gregory explained.

At first, the team applied the airway pressure through a tube in the infant's trachea, but they came to prefer a small pressure chamber over the head only, like a tiny diving helmet, which has since become widely known as the "Gregory box." With either approach, humidified oxygen or high-oxygen air is forced in continuously at slightly elevated pressures (up to 14 millimeters of mercury). The Gregory box is also equipped with an anesthesia bag to permit artificially assisted breathing if necessary. With CPAP alone, the infant breathes spontaneously.

The effect on most of the struggling infants is dramatic and immediate, with relief obvious. Holding the collapsed lungs steadily open, CPAP extends

(more)

the lung surface area so desperately needed to oxygenate the blood, and the measure of oxygen tension in the blood ($PO_2$) soars toward normal, often doubling in minutes. CPAP therapy is technically complicated, professionally challenging, and costly--a nurse for each baby is needed, according to some authorities. However, if CPAP and associated artificial ventilation can be sustained long enough (a week or so is about average, although a month or more is possible) most newborns with the syndrome gradually acquire the ability to breathe normally. For Dr. Gregory and his co-authors in San Francisco, the success rate now exceeds 90 percent--a figure unimaginable 10 years ago.

Dr. Gregory's research was supported by grants from the National Heart and Lung Institute, the National Institute of General Medical Sciences, and the National Institute of Child Health and Human Development.

#

VENEREAL DISEASES--Several years ago, scientists thought that the use of antibiotics had finally brought venereal diseases under control. However, in recent years, the incidence has reached epidemic proportions. In order to cope with this serious public health problem, the National Institute of Allergy and Infectious Diseases is encouraging more research on the biology and immunology of the organisms causing sexually-transmitted diseases.

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News Feature

## NIH SCIENTISTS DEVELOP IMPROVED METHOD TO STOP PARATHYROID DISEASE

Early and detailed diagnosis is often the key to effective treatment of important diseases. More patients with chronic diseases could be effectively treated if the afflictions were detected in early stages and the site and extent of involvement precisely determined. Parathyroid disease, an endocrine disorder being diagnosed with increasing frequency in this country, is an example.

The parathyroids are tiny hormone-secreting glands located in the neck behind the thyroid. Parathyroid hormone is responsible for metabolism of calcium and phosphorus in the body. When a tumor or other disorder causes the parathyroid to secrete too much hormone, loss of calcium in the bones results in progressive pain, tenderness, spontaneous fractures, muscular weakness, and abdominal disorders.

With surgery to remove the diseased tissue, the prognosis for patients with hyperparathyroidism is excellent. However, the size and varying location of the glands make them difficult to locate, and surgery therefore may not always be successful.

Health screening tests that detect elevated calcium levels in the blood before other symptoms of hyperparathyroidism appear are now in use. This means that the disease is diagnosed earlier, when the glands are even smaller and more difficult to find at surgery.

Recently, investigators at the NIH Clinical Center (including staff doctors of the National Cancer Institute and National Institute of Arthritis, Metabolism, and Digestive Diseases) have developed a method of locating the

(more)

diseased glands that has been accurate in nearly 100 percent of patients with newly-diagnosed disease, and in over 80 percent of those for whom earlier treatment failed.

The method is called selective venous catheterization and uses a radioimmunoassay test to measure parathyroid hormone in the blood. Difficult-to-find parathyroid adenomas, for instance, are located by looking for increasing levels of the hormone in the veins of the neck and upper chest as the catheter tip gets closer and closer to the malfunctioning gland.

The veins are explored using a fluoroscopically directed catheter in the tributaries that drain the thyroid gland and the surrounding tissues. In these veins, elevations of parathyroid hormone several times the peripheral blood level correlate with the location of the gland or tumor, and suggest whether multiple glands are involved in the overproduction of hormones.

In patients who have undergone prior parathyroid surgery, the vein system is sometimes altered or removed and alternate routes established to drain the area. In such instances, arteriography, a procedure in which a dye or marker is injected into the arteries, is performed to locate the alternate pathways.

The procedure takes several hours, but enables physicians to fix the precise location of the gland and forewarn surgeons of any difficult situations.

#

News Feature

## NINCDS REVIEWS RISK OF STROKES IN LONG-TERM BLOOD PRESSURE REDUCTION

The increasing use of drugs to control hypertension is accepted as one of the reasons for the gradually increasing survival rates from stroke, and for a gradually decreasing incidence. Many physicians, however, have been uncertain about the safety of antihypertensive drug therapy in patients who already have had strokes. They have felt that drastically lowering blood pressure might be disastrous in a patient whose cerebral circulation already has been reduced. And they have hesitated to interfere with a situation to which the cerebral blood vessels may have gradually adjusted.

These fears should be reduced and standards of therapy improved by the results of a large-scale cooperative study reported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) grantees. The scientists have found that long-term reduction of blood pressure does not increase the risk of stroke recurrence, and have established a basis for recommending antihypertensive drugs for stroke patients even if they have only moderately elevated blood pressure. The group also has confirmed that antihypertensive drug therapy in stroke patients reduces the risk of congestive heart failure.

The study was the first to provide these types of data from a group of people with mild to moderate hypertension. Patients in this category are often not undergoing any hypertensive treatment.

Ten university medical centers and large hospitals joined in the study and a central registry was set up at the University of Michigan Medical Center. A medical risk review section monitored the study quarterly to

(more)

Stroke Risk (Cont'd)

determine any possible events indicating undue risk. Each center set up a separate stroke-hypertension clinic, with an internist and a neurologist in charge.

There were 452 stroke survivors with recumbent blood pressures in the mild to moderate ranges (readings from 140 to 220 millimeters of mercury systolic and 90 to 115 millimeters diastolic pressure) observed for a mean period of three years. Half of these received antihypertensive drugs and half received placebos, inert medication. Drugs used were a combination of deserpidine and methyclothiazide. There were 37 stroke recurrences in the drug-treated group, and 42 in the placebo-treated group. This was not a statistically striking difference, but a clear demonstration of safety, and a good indication that these drugs are beneficial.

Stroke is the third largest cause of death and the leading cause of long-term disability in the United States. Each year about 500,000 Americans are stricken, and about 200,000 die. There are about two million stroke survivors in the country, with varying degrees of disability.

An extensive effort is being made to develop surgical procedures and drugs to lessen the effects of stroke. Since brain cells cannot survive an interruption of blood supply for more than a few minutes and can never be replaced, after-the-fact measures probably will never do more than halt continuing brain damage. Prevention thus becomes a more effective goal. The prospect of being able to prevent many thousands of strokes within the next few years was raised when a Veterans Administration study definitely established that drug treatment of high blood pressure can bring about a great reduction in deaths from strokes. The NINCDS study provides valuable data for physicians concerned with prevention of second strokes.

#

News Feature

## DOSE OF HARMLESS BACTERIA MAY CONFER SOME IMMUNITY

Recent research by National Institute of Child Health and Human Development scientists may be effective in lowering the incidence of acquired mental retardation, and provide a basis for revising current theories about how we acquire natural immunity.

Scientists led by John B. Robbins, M.D., believe their recent findings strongly suggest that immunity against meningitis and other critical diseases may be safely stimulated by feeding newborns with a single dose of live, harmless bacteria.

Such immunity would be of great importance because the bacteria being studied--*Hemophilus influenzae* type B and groups of meningococci and pneumococci--can all cause meningitis, inflammation of the covering of the brain. *H. influenzae* type B, for example, causes about 12,000 to 15,000 cases of meningitis in infants and young children annually.

Between 30 to 50 percent of the victims who recover after treatment with antibiotics suffer permanent disability, including mental retardation, making this disease the leading cause of acquired mental retardation in the United States.

Recently the scientists found that they could cause antibody formation against *H. influenzae* type B in animals by feeding them a harmless strain of *Escherichia coli*, bacteria normally growing in the human and animal intestine. The antibody response was great enough to protect against a deadly challenge from the *H. influenzae* type B organism.

(more)

Harmless Bacteria (Cont'd)

Protection was due to a so-called cross-reaction response, which was possible because the outer coating antigens of *E. coli* and the *H. influenzae* type B are so similar biochemically that they evoke nearly identical antibody formation. The outer coating antigens, when absorbed from the intestinal tract, act as signals to the body that antibodies should be produced to fight off a foreign organism.

Stimulated by the success with *E. coli* in conferring cross-immunity to *H. influenzae* type B, the scientists began a search for common, harmless organisms which would cross-react with other disease-producing bacteria, that is, Groups A and C *Neiserria meningitidis* and Types I and II *Diplococcus pneumoniae*. They have now found several harmless bacteria, the antigens of which cross-react with one or the other of these two bacterial types. Again, cross-reaction is due to similarity in biochemical structure. Growing the benign bacteria in the intestine of the animals produced potent antibodies to the disease-causing bacteria.

This finding suggests that some of the common, harmless bacteria of the intestine may be the source of natural immunity against many of the disease-producing bacteria developed by most persons before they reach late childhood. This concept differs from the traditional concept, which holds that natural immunity is evoked by a challenge from the disease-producing bacteria that is so mild as to cause no symptoms. The new concept could also explain why most adults and children over six years of age have serum antibodies to *H. influenzae* type B, although the organism is rarely found in nose, pharynx, or rectal cultures.

(more)

Harmless Bacteria (Cont'd)

The scientists believe that it might eventually be possible to stimulate the growth of a colony of such harmless bacteria in the small intestine of very young infants (who have not developed their own natural immunity) in order to protect them from several bacterial diseases. They believe that a single feeding of the harmless bacteria would accelerate the development of adult immunity, usually not attained until about six years of age. Therefore, a child would be protected over the span of years between the time when antibodies acquired prenatally from his mother's circulation have ceased to guard him and the time he would otherwise fortuitously acquire natural immunity.

#

HOSPITAL-ASSOCIATED INFECTIONS--Five out of every 100 hospitalized persons acquire new hospital-related infections. Some of these are the result of a breakdown in the patient's own protective mechanisms against disease. Others are related to procedures necessary to hospital care. The National Institute of Allergy and Infectious Diseases is supporting studies on several aspects of this complex problem, including urinary tract infections (which account for about 35 percent of all hospital-related infections) and drug-resistant organisms.

#

News Feature

# MUSCULAR DYSTROPHY WEAKENS CHILDREN'S SKELETAL MUSCLES

Muscular dystrophy (MD) usually begins in childhood but it can attack persons of all ages. It affects over 200,000 people in the United States.

MD is a progressive, wasting disease that weakens the "voluntary" or "skeletal" muscles--those on the outside of the body--such as the biceps that youngsters show by flexing their arms.

A toddler may be average in play activities and talk normally, but a few months later, this same youngster can become clumsy, then weaker, and eventually helpless. Usually, there is no pain with the disease in children. MD patients also retain the use of their fingers, since the last muscles affected are the small ones of the hand.

Because MD is an inherited disorder, it is important that the physician have a precise medical history as well as any family history of the disease. Blood and urine tests, muscle biopsies, X-rays, and tissue cultures aid in diagnosing muscular dystrophy. It is not contagious.

The most prevalent form of MD (Duchenne) is a sex-linked, genetic trait carried by women who show no symptoms themselves. There is, however, a 50 percent chance that male offspring will be afflicted and a 50 percent chance that female offspring will be carriers.

Scientists conducting research with support from the National Institute of Neurological and Communicative Disorders and Stroke have developed a technique that identifies carriers of the gene for the progressive type of MD.

In other studies scientists reported in 1957 that selenium deficiency caused rats to develop severe liver damage, and conversely that selenium prevents a fatal blood disease in young chickens. Selenium, a nonmetallic

(more)

element, is an essential nutrient in very small quantities, for animals and bacteria. White muscle disease, a form of muscular dystrophy in cattle and sheep, also became widely recognized as a selenium-deficiency disease.

In 1973, it was shown that selenium is an essential part of an enzyme in red blood cells that protects these cells from damage by harmful oxidizing agents (peroxides) and from radiation damage. This enzyme, glutathione peroxidase, normally is found in the red blood cells of cattle, sheep, poultry, rats, and, presumably, man, but in selenium-deficient animals the enzyme is missing. Similarly, a small protein that contains selenium has been reported to occur in the muscles of healthy lambs, but selenium-deficient lambs suffering from white muscle disease lack this protein.

In 1974, Thressa C. Stadtman, Ph.D., of the National Heart and Lung Institute, isolated a new selenoprotein from a bacterium, *Clostridium sticklandii*, that she discovered several years ago. The bacterial selenoprotein is an enzyme that furnishes energy for growth of the microorganism and is similar in size to the lamb muscle selenoprotein.

Thus, the bacterial and the muscle selenoproteins may have a similar function in reactions essential to growth. The bacterial selenoprotein is easier to obtain in pure form and in quantities necessary for detailed study than is the muscle protein. It therefore may prove to be useful in research on certain types of muscular dystrophy.

#

News Feature

# PHANTOM HEAD USED IN STUDY OF ABSORBED X-RADIATION

A recent study of absorbed X-radiation delivered to a phantom head by seven intraoral radiographic techniques confirms that operation at 65 KVP (kilovoltage peak) delivers less total dose than at 90 KVP when a 16.5 inch radiation source to skin distance (SSD) and an open-end cylinder is used.

However, use of an 8.5 SSD results in a lesser dose when the 90 KVP is employed. Entrance dose is minimized when higher KVP techniques are used.

Of perhaps greater significance than the kilovoltage effect (65 versus 90 KVP) is the fact that use of open-end cylinders rather than pointed plastic cones results in lower total dose regardless of kilovoltage. Peak kilovoltages of 50 and the widely diverging radiation beam used with low kilovoltage X-ray equipment combine to give the highest total dose.

The clinical objective of work by Neal W. Frey, D.D.S., M.S., and Arthur H. Wuehrmann, D.M.D., whose work is supported by the National Institute of Dental Research, was to determine comparative dose distributions delivered to the patient's head by the seven intraoral radiographic techniques. Measurement of intrabeam and extrabeam doses required selection of numerous dosimeter sites within a phantom head. All doses were comparably measured using thermoluminescent techniques.

Site selection for dosimeters was based on orientation of the primary X-ray beam within the head for each technique as determined by exposure of nonscreen films. The beams were represented by well-delineated areas of blackening on exposed sheets of X-ray film placed between horizontal sections of the phantom. A thermoluminescent dosimetry system was utilized to obtain

(more)

internal and external dose measurements for comparison among radiographic techniques.

Doses measured at the plane of the film ranged from 70.35 to 79.95 mrads for all except the 50 KVP technique, which required a dose of 95.75 mrads. The high dose recorded for the latter technique may indicate film energy dependence at low photon energies as well as divergent beam geometry associated with the short cone technique.

Film dose as a percentage of entrance dose was greater than 40 for all long cone techniques involving KVP's greater than 65. The least favorable percentage, 20 percent, was recorded for the short cone 50 KVP technique.

The scientists reported on their work in the dental radiology section of *Oral Surgery, Oral Medicine, Oral Pathology* for July and October 1974.

#

**IMMUNOLOGIC PROBLEMS**--In addition to allergic individuals, other patients with immunologic problems include those with immune deficiency diseases (such as agammaglobulinemia) or organ transplants. An individual's immunity to infectious disease is based primarily on the interaction of antigens, antibodies, and specialized cells called lymphocytes. A more precise understanding of these components and how they interact is the aim of many varied research projects of the National Institute of Allergy and Infectious Diseases.

#

## News Releases Issued

PRESSURE CHECKING--The Missouri State Dental Association adopted in May, 1975, a resolution that encourages member dentists to take blood pressure readings on all patients as a routine part of the dental examination; encourages members to refer all patients with elevated blood pressure to their regular physicians or usual sources of medical care for appropriate workup or treatment; and encourages schools of dentistry or schools training dental aides or hygienists throughout the State to include in their curricula: basic information on high blood pressure, training in taking and recording blood pressure, and procedures for referring patients with elevated readings to appropriate sources of medical care.

Under the resolution, the dentist neither makes a definitive diagnosis nor does he prescribe or supervise treatment, should this be necessary, explained the National Heart and Lung Institute.

#

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Research Advances

## LIGHT-SCATTERING METHOD USED IN STUDY OF CORNEA

Scientists at the Johns Hopkins University Applied Physics Laboratory (APL) are performing unique studies to probe the structure of the eye's cornea, the clear front covering of the eye. By measuring the way light is scattered as it passes through the cornea, they have been able to learn more about its several layers. The various structures that make up these layers are responsible for the transparency of the cornea and their disruption gives rise to vision loss.

Richard A. Farrell, Ph.D., and Russell L. McCally of Johns Hopkins reported their findings to the Biological Physics Division of the American Physical Society at their March 31, 1975 meeting in Denver, Colorado. In their paper, "Dependence of Light Scattering on the Depth into the Normal Rabbit Cornea," Dr. Farrell explained that "light scattering affords a non-invasive probe of corneal structure that has the ultimate potential of being used in the intact eye. It also has the advantage that laboratory experiments are performed on fresh unstained tissues."

The Johns Hopkins scientists pointed out that their research, which is supported by the National Eye Institute, is primarily aimed at understanding structures within the stromal region which comprises 90 percent of the thickness of the cornea.

"The problem," explained Dr. Farrell, "is that the stroma is sandwiched between two thin cellular layers, the epithelium on the front and the endothelium on the back, and, according to some other investigators, these layers and not the stroma are the main source of scattering in the cornea."

In their paper, Farrell and McCally note that "the measuring apparatus

(more)

distorts the actual scattering so that the scattering from closely lying layers becomes mixed together. The effect is analogous to trying to listen to two radio stations which are very close on the dial using an inexpensive radio -- what you hear is a composite of both.

"The earlier researchers did not account for this mixing and what we have done is to unravel the different components. When properly unscrambled, these measurements in fact show that the stroma does the bulk of the scattering."

In addition to explaining the measurements of the earlier researchers, the Hopkins team also presented their own measurements which showed that under a great variety of conditions, the stroma is the primary scatterer.

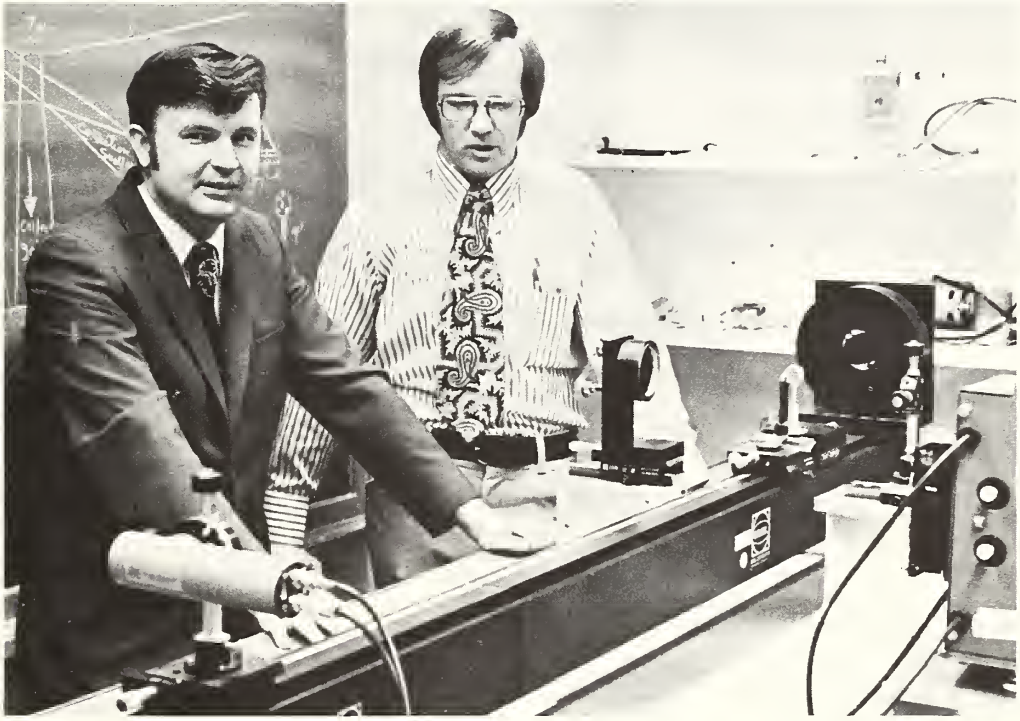
The stroma is composed of collagen fibrils which lie parallel to the corneal surfaces. These rod-like protein fibrils have the role of helping the eye keep its shape and possess the mechanical strength necessary to resist the intraocular pressure. Anchored in the wall of the eye (scleral ring), they run through the cornea in much the same manner as reinforcing rods in concrete. The individual fibrils are too small to be seen by the light microscope, but are easily seen with the more powerful electron microscope. However, because they are so numerous, the rods would be expected to scatter much of the light incident on the cornea.

The problems were first introduced to the APL group by M. E. Langham, Ph.D., of the Wilmer Institute of the Johns Hopkins Medical Institutions. Shortly afterward, Dr. Farrell, in collaboration with I. W. Hart, Ph.D., who is the chairman of the research center at APL, showed for the first time that corneal transparency is a consequence of the semi-ordered arrangement of fibrils as

(more)

seen in the electron microscope.

Stimulated by that study, Dr. Farrell and Mr. McCally demonstrated in a subsequent paper that the characteristic way in which the cornea scattered light of different colors could be used to confirm the structures shown in electron micrographs. This result presumed that the stroma is the primary source of scattering and Dr. Farrell summarized their latest findings as "confirming that scattered light contains important information about stromal structure, and as reinforcing our confidence that our methodology is appropriate for extracting that information."



*Dr. R.A. Farrell (left) and R.L. McCally of The Johns Hopkins University Applied Physics Laboratory are studying the way the cornea of the eye scatters light to probe its fundamental structure. The various structures within the cornea are responsible for its transparency and their disruption gives rise to vision loss. The Hopkins scientists are pictured with the experimental apparatus, which will be used to measure light scattered at small angles from various depths within the corneas of rabbit eyes. (NIH Photo #1397)*

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Research Advances

# INFANTILE DIARRHEA STUDY HELPED BY CALF VIRUS TEST

National Institute of Allergy and Infectious Diseases (NIAID) scientists and others, using a calf diarrhea virus as antigen, have developed a new complement fixation test for the human reovirus-like agent of infantile gastroenteritis. The ready availability of this culture-grown Nebraska calf diarrhea virus (NCDV) and its ability to serve as a "substitute" for the human agent, which cannot yet be cultured in quantity, should greatly facilitate epidemiologic studies of infantile diarrhea.

In addition, the team of investigators, led by Albert Z. Kapikian, M.D., of NIAID's Laboratory of Infectious Diseases, observed in the course of their studies that a large proportion of children infected with the human agent developed serologic evidence of infection with the calf agent as well. This observation raises the possibility that immunization against human disease might be accomplished by use of the calf virus. An orally-administered attenuated NCDV vaccine is already in use in veterinary medicine.

Acute infectious gastroenteritis has long been one of the commonest causes of childhood illness and in many parts of the world is a leading cause of infant death. It has been estimated that probably no more than one-eighth of the world's infants and children are free from appreciable risk of lethal diarrhea. Although some cases of acute gastroenteritis can be attributed to bacteria or parasites, an even more important cause, according to medical investigators in a number of countries, may be the new reovirus-like agent.

(more)

In the present study, the scientists found that six out of eight children who shed the human agent in stools and demonstrated serologic evidence of infection to the human agent, also demonstrated serologic evidence of infection when a concentrated calf virus preparation was used as the complement fixation antigen. In a separate serologic survey of residents of a children's institution, the investigators found that antibody appeared in the sera of over 80 percent of individuals by 36 months of age. Thus, members of this young age group, who are at high risk of developing severe diarrheal disease, would be prime candidates for immunoprophylaxis when, and if, a safe, effective vaccine is developed for the new reovirus-like agent.

Results of these studies were reported in the May 10, 1975, issue of *Lancet* by Albert Z. Kapikian, W. Lee Cline, Richard G. Wyatt, Anthony R. Kalica, Harvey D. James, Jr., Dale Van Kirk, and Robert M. Chanock, Laboratory of Infectious Diseases, NIAID; Charles A. Mebus, Department of Veterinary Science, University of Nebraska, Lincoln; and Hyun Wha Kim, Children's Hospital National Medical Center, Washington, D.C.

#

RHEUMATIC FEVER--Although the cause of rheumatic fever is not fully known, research has shown that most rheumatic fever cases are preceded by "strep" infections of the throat, nose, or tonsils, according to the National Institutes of Health.

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June 25, 1975

Research Advances

# SEPTIC ARTHRITIS TREATED BY NEW NEEDLE ASPIRATION METHOD

A Boston University scientist has found that more patients with septic arthritis recover completely following initial treatment of the affected joint by needle aspiration, compared to patients treated initially by surgical drainage of the joint.

Alan S. Cohen, M.D., of Boston University, and his associates reported their findings in *Arthritis and Rheumatism*, February 1975. Dr. Cohen's research is supported by a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Successful treatment of patients with acute infectious arthritis requires appropriate antimicrobial therapy and removal of purulent material from the joint. Classically, such drainage has been accomplished surgically, although needle aspiration has proved effective in recent years. Controversy currently exists concerning which mode of drainage should be employed initially.

Dr. Cohen's retrospective study has evaluated both procedures as initial modes of drainage in 59 patients with acute septic arthritis. While full recovery was noted in 42 percent of patients treated surgically at the outset, 67 percent of those treated by needle aspiration recovered completely despite the greater prevalence in this group of adverse host factors. Thus, it would appear that needle aspiration is preferable as the initial mode of drainage, except in cases of hip infection, which require surgical drainage.

The case records of 59 patients with infectious arthritis who were seen at Boston City Hospital and University Hospital between 1965 and 1972 were examined. All patients received parenteral antibiotics. In 42 patients, the

(more)

infected joint was drained from the outset by repeated needle aspirations, while 17 patients underwent immediate surgical drainage. Eighty percent of the patients were followed up for at least three months.

Complete recovery occurred in 7 of 17 patients (42 percent) operated on at the outset, and in 28 of 42 patients (67 percent) whose joints were drained by needle aspiration. Moreover, 37 of 46 joints (80 percent) drained by needle aspiration, but only 8 of 17 joints (47 percent) treated by initial surgical drainage, showed complete recovery. Patients undergoing needle aspiration had a greater prevalence of serious underlying illness, concomitant extraarticular infection, prior arthritis in the infected joint, and recent antibiotic or immunosuppressive therapy.

Results of this study also point up the necessity of instituting therapy immediately following a diagnosis of septic arthritis, because recovery was complete in only three of 11 patients with symptoms of infection for more than seven days prior to initiating therapy.

#

SORE THROAT--Penicillin and certain other antibiotics are effective destroyers of the streptococcus germ. Used promptly according to the doctor's orders whenever a sore throat or tonsillitis strikes, they can usually prevent the first attack of rheumatic fever, according to the National Institutes of Health.

#

Photo Feature

# CHENIC ACID THERAPY MAY REPLACE SURGICAL TREATMENT OF GALLSTONES

The possibility of dissolving gallstones in the human body is closer now than ever before due to the research being conducted at the Mayo Clinic. Fifteen years of concentrated research on bile acids by Alan F. Hofmann, M.D., Associate Director of the Gastroenterology Unit, may come to fruition as the feasibility of using a pharmacological substance to dissolve gallstones emerges.

The compound, chenodeoxycholic acid (chenic acid), is a natural bile acid in man. Oral dosage of chenic acid to effect bile acid balance in the body may ultimately be commonly prescribed as nonsurgical therapy for cholesterol gallstones, says Dr. Hofmann. His work with Johnson L. Thistle, M.D., another Mayo Clinic researcher, may eliminate the necessity of high-risk patients having to undergo cholecystectomies (gallstone operations).

Dr. Hofmann firmly believes that the medical conquest of cholesterol gallstones is fast approaching. "In the future, gallstones should be detected much earlier because of improvements in ultrasound techniques," he says. "High-risk individuals may be detected by studies on bile acid metabolism before the patient gets gallstones, and prophylactic therapy initiated. New techniques will be developed for *in situ* dissolution of common duct stones."

A controlled clinical trial, utilizing chenic acid dosage, was conducted with 30 men and 26 women at the Mayo General Clinical Research Center, which is supported by NIH's Division of Research Resources. After six months,

(more)

more than half of the patients showed reduction in gallstone size. Subsequent X-rays revealed the gallstones had disappeared in 13 of the patients.

Gallstones are caused by a cholesterol oversaturation of the bile in the human body. Cholesterol is kept in solution by two other components of the bile: lecithin and bile acids. When the ratio of cholesterol to lecithin and bile acids is too great, gallstones form. If the concentration of bile acids can be increased, the cholesterol will again become soluble and the gallstones will dissolve.

The chenic acid dosage technique attempts to achieve proper equilibrium between the components of the bile. Since Dr. Hofmann feels that factors determining the saturation of bile are still not thoroughly understood, he and his coworkers are continually conducting intensive investigations at Mayo Clinic.

Dr. Hofmann has been a proponent of chenic acid therapy since his initial studies as a research associate at Rockefeller Institute. He is internationally recognized as a leader in this area and was chairman of a workshop on chenic acid therapy of gallstones held in Freiburg, West Germany, in 1973.

The concept of cholesterol gallstone dissolution by oral dosage of chenic acid is gathering momentum in clinical research circles. Going deeper into controlled toxicity studies of chenic acid dosage, a national cooperative trial has been funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases which calls for the establishment of ten

(more)

gallstone study centers throughout the country. Approximately 100 patients will be treated in each center. Leslie J. Shoenfield, M.D., Director of Gastroenterology at the Cedars-Sinai Medical Center in Los Angeles, has been appointed coordinator of this program.

"The status of chenic acid at present may be compared with that of the first contraceptive pill," Dr. Hofmann says. "The important event that has occurred is that the feasibility of a medical approach to gallstone dissolution has been demonstrated. As far as I know, from published literature, no other compound has induced gallstone dissolution."

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OF RELATED INTEREST
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Research Advances

## PRIMARY BILE ACID MAY DISSOLVE GALLSTONES

Scientists of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have shown that chenodeoxycholic acid (CDCA) acts to reduce the lithogenicity of bile, and dissolve cholesterol gallstones, by decreasing the hepatic secretion of cholesterol. It was not previously known if decreased bile lithogenicity results from increased hepatic secretion of bile acids or lecithin, or from decreased secretion of cholesterol.

This finding sheds light on the mechanism of action of CDCA, a primary bile acid, and suggests that relatively low doses might achieve therapeutic effects without significant adverse effects. Such an approach will be considered in the long-term clinical trials of CDCA therapy for gallstones planned by the NIAMDD.

Hepatic secretion rates of biliary lipids and pool sizes of bile acids were examined in ten healthy volunteer subjects without gallstones before and after the feeding of relatively low doses of CDCA, usually 500 mg/day. In five subjects, the effects of CDCA were compared to those of cholic acid, a bile acid that apparently does not dissolve gallstones.

Low doses of CDCA consistently reduced the lithogenicity of bile by decreasing the proportion of cholesterol relative to the solubilizing bile components and lipids -- bile acids and lecithin. This decrease was secondary to a reduction in hepatic secretion rate of cholesterol, while secretion rates of bile acids and lecithin remain unchanged. Cholic acid did not affect the lithogenicity of bile or hepatic secretion rates of cholesterol.

The authors speculate that decreased hepatic secretion of cholesterol is

(more)

secondary to either reduced synthesis or reduced intestinal reabsorption of cholesterol. Scott M. Grundy, M.D., Ph.D., and associates of NIAMDD's Phoenix Clinical Research Section reported their findings in *Gastroenterology*, March, 1975.

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OF RELATED INTEREST

is the article that

precedes this story.

June 25, 1975

Research Advances

## AMINO ACIDS INHIBIT BLOOD CELL SICKLING

Three amino acids (part of the protein building blocks of cells) may be useful in the control of sickle cell anemia. The amino acids--asparagine, glutamine, and homoserine--have been shown to inhibit the "sickling" that occurs in the red blood cells of persons with sickle cell anemia.

In sickle cell anemia the twisted or sickled red cells sometime stick together and form a "log-jam" or obstruction of the small blood vessels. This in turn blocks the flow of blood to the surrounding tissues while the breakdown of these cells results in anemia.

Nevenka Rumen, Ph.D., a guest worker at the Reproductive Research Branch of the National Institute of Child Health and Human Development, presented these research findings at the annual meeting of the Federation of American Societies for Experimental Biology, April 1975.

In her presentation, Dr. Rumen discussed that ability of these amino acids to reverse the sickling of the abnormal red cells (hemoglobin S and S-C). The experiments were carried out with cells from sickle cell patients. In all cases (10 different sets of cells) sickling was inhibited over 90 percent of the time by each of the three amino acids. Studies are being conducted currently to determine the mechanism of action of each of the amino acids. The successful use of these neutral amino acids might in the future mean that prevention of a sickle cell crisis could be accomplished by dietary means.

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Photo Feature

## CULTURES OF BONE MARROW PREDICT LEUKEMIA RELAPSE

Cultures of bone marrow cells now enable physicians to predict the relapse of a leukemia patient three or four weeks in advance, according to research by Kamran Tebbi, M.D., a pediatric hematologist at the Case Western Reserve University School of Medicine.

Knowledge of an impending relapse (reappearance of leukemia symptoms) enables doctors to begin treatment before the relapse, and to delay or possibly forestall it.

Leukemia diagnosis is made from studies of the patient's bone marrow, where the abnormality is thought to originate. Dr. Tebbi believes that clues to a leukemia cure lie in the study of blasts, immature cells that become the "parents" of the white cells and red cells. Blasts normally develop into colonies when cultured in test tubes.

"While a normal person's marrow contains fewer than five percent blasts," said Dr. Tebbi, "that of a leukemia patient is largely replaced by blast forms. If we put leukemic bone marrow, which contains mostly blasts, into a special culture solution, there is zero growth, but we don't know why."

This lack of culture growth is useful, however, for indicating that remission (abatement of leukemia symptoms) is about to end in a patient with apparent good health and seemingly normal marrow. With this knowledge, hematologists can intensify chemotherapy before the appearance of relapse.

This procedure, says Dr. Tebbi, is more effective with children than adults.

(more)

Leukemia (Cont'd)

Dr. Tebbi and others are at work trying to discover ways of stimulating leukemic cells to grow normally. They have isolated a substance, colony stimulating activity (CSA), that stimulates growth from certain types of cells in normal human blood and bone marrow.

"When CSA is added to normal bone marrow," says Dr. Tebbi, "the cells grow in large numbers. It even has some effect on leukemic cells. We know now that we can stimulate leukemic cells to at least limited growth and differentiation in the test tube.

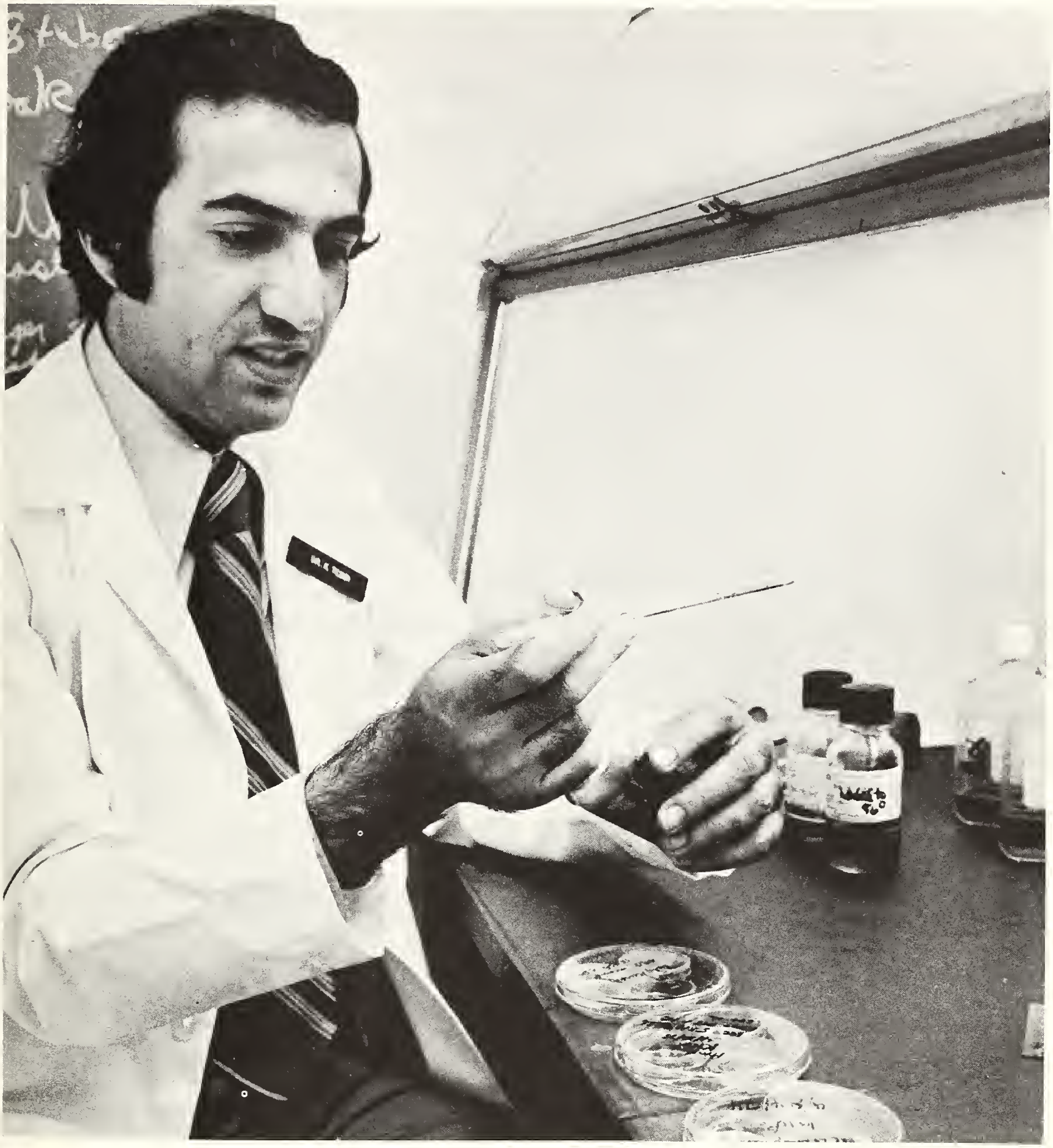
"But we're trying to find better stimulators," he said. "If leukemic cells can be stimulated enough, we hope that they will produce normally. And that's a real hope for the future."

Dr. Tebbi's research work has been funded by a General Research Support Grant from the NIH Division of Research Resources.

*Kamran Tebbi, M.D., is viewing red blood cells on a television microscope. He is studying ways to predict the impending relapse of a leukemia patient. (NIH Photo #1398)*

(more)

Leukemia (Cont'd)



*Dr. Tebbi is withdrawing a solution from a bottle during his study of cultures of bone marrow cells. His research is funded by the Division of Research Resources. (NIH Photo #1399)*

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NEWS & FEATURES From NIH June 25, 1975

Photo Feature

## SEA SLUG USEFUL FOR STUDY OF NERVOUS SYSTEM BIOLOGY

Extensive studies for culturing several species of the shell-less slug *Aplysia* are currently being conducted at the Kewalo Marine Laboratory of the University of Hawaii's Pacific Biomedical Research Center, and at the Pacific Bio-Marine Supply Company of Venice, California, under contracts with the NIH Division of Research Resources (DRR).

The sea slug, or sea hare, has become an important research animal for studies on the biology of the nervous system because of the low number of cells in the brain and other portions of the nervous system in the animal.

The formal culturing (reproduction of several generations) of *Aplysia* species would represent an important contribution to biomedical researchers dependent on the use of these organisms.

The availability and quality of these organisms in their native habitats has diminished significantly during the past several years. The DRR is supporting these two studies in efforts to develop methods which can be employed to assure adequate resources of defined strains of *Aplysia* for biomedical researchers in the future.

In California, Rimmon C. Fay, Ph. D., and James A. Vallee, Ph. D., are culturing the *Aplysia californica* species, the most common sea hare used by neurological researchers in the U.S. They are also conducting mariculture work on several other related species native to the West Coast of interest to researchers.

(more)

In Hawaii, Michael G. Hadfield, Ph. D. and Assistant Researcher Marilyn S. Dunlap are concentrating on *Aplysia juliana* and other related species common to the tropical waters in the area. The ultimate objective of their investigation is to perfect developmental techniques for continuous rearing of the species. The studies include growth rate and longevity, reproductive biology, development, and nutrition of *Aplysia juliana*.

"We have already determined what foods (seaweeds) the animals eat in nature and have found that these seaweeds are acceptable foods, even after being freeze dried," Dr. Hadfield reports.

Other foods for developing the sea hares have also been investigated at the Hawaiian laboratory. Their studies have shown that well-fed *Aplysia* will grow at prodigious rates (weight gains of 13,000 percent in two weeks), and can reproduce in as little as one or two months after hatching from the egg. These animals lay up to 250 million eggs in a lifetime of six months or longer. When they first hatch from gelatinous egg masses, the young *Aplysia* are swimming larvae, very different in appearance and habit from the sluggish bottom-living adults.

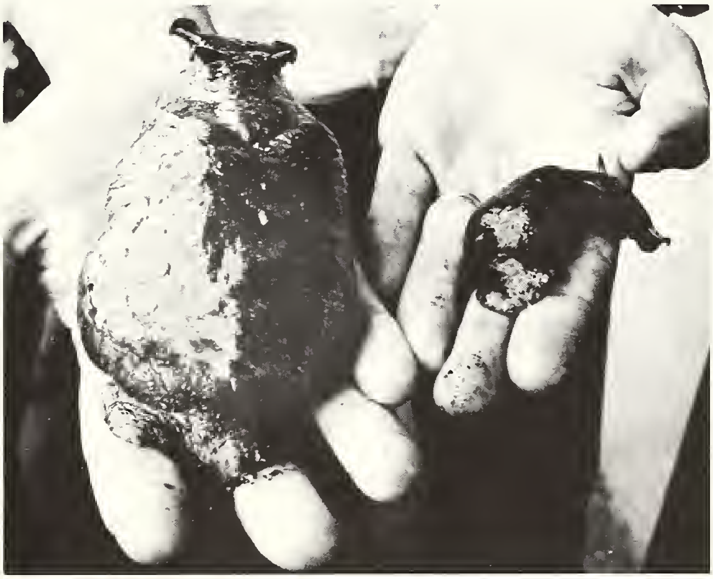
The major problem of continuous rearing of *Aplysia*, reports Dr. Hadfield, is culturing the larvae for the approximate one-month period which they require before taking up their sea bottom existence. The Hawaiian mariculture researchers have maintained larvae under tightly regimented conditions of light and feeding.

(more)

Sea Slug (Cont'd)

Both marine research groups will endeavor to raise *Aplysia* in artificial sea water in the laboratory. If these techniques prove successful, the scientific community will be able to raise and maintain *Aplysia* in their own laboratories at will. This accomplishment will spark impetus for increased and accelerated work on nerve transmission of messages in the body, sensory stimuli to the central nervous system, and other related physiological functions.

These mariculture projects should ultimately aid neurological researchers in their quest for a better understanding and treatment of malfunction of the central nervous system in the human body.



*These two sea hares, each of which is two to three months old, show how much larger a sea hare can grow in a laboratory. The sea hare at right is the average size at that age of those usually found. The one at left was cultivated in the Kewalo Marine Laboratory of the University of Hawaii. This mariculture work is supported by the NIH Division of Research Resources. (NIH Photo #1400)*

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NEWS & FEATURES From NIH June 25, 1975

News Feature

## NIDR SURVEYS ATTITUDES ABOUT PLASTIC SEALANTS

A survey of 4,000 representative practicing dentists in the United States, 87 percent of whom responded, shows that those who graduated before 1950, and those who stress prevention or work chiefly with children, are more likely than other dentists to believe that plastic sealants are valuable for protecting the chewing surfaces of teeth from decay, and to use the procedure regularly.

John J. Hefferen, Ph.D., of the American Dental Association reported the findings on attitudes towards and use of sealants on April 12, 1975, at the 53rd General Session of the International Association for Dental Research meeting here. The sealant study is part of a larger survey, funded by the American Dental Association and the National Institute of Dental Research, which was designed to learn more about current attitudes and activities of dentists towards preventing tooth decay.

There were two reasons, Dr. Hefferen said, that most dentists gave for not using sealants: first, that research has not yet proved their value, and second, that sealants do not last long enough in the mouth. Other dentists feared that decay can be sealed in as well as out. Some considered that the equipment and materials are too costly, while others were not familiar with the procedure. Few thought that it took too much time.

Since 17 percent of the dentists surveyed said they were unaware of the value of sealant and 65 percent thought the value to be moderate or slight, Dr. Hefferen said it is not surprising that 62 percent of them do not use sealants. The survey indicates that dentists in the Northeast and Midwest

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areas of the country are more likely to use sealants than those in the Southeast or Far West.

If sealants are to achieve their potential for preventing decay, Dr. Hefferen suggests that communication with the practicing dentists must be improved.

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**HEPATITIS**--Viral hepatitis occurs in at least two distinct forms. A person acquires hepatitis A, or infectious hepatitis, by direct contact with an infected person or by contaminated food or water. The virus of hepatitis B, or serum hepatitis, is usually transmitted by the transfusion of blood or inoculation of blood products from infected persons. Recent evidence indicates that yet another agent, or agents, may also cause post-transfusion hepatitis. A major research effort is under way at the National Institute of Allergy and Infectious Diseases to increase understanding of the causes of hepatitis and to hasten vaccine development and production.

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Photo Feature

# NLM PRIZES COLLECTION OF RARE MEDICAL BOOKS

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ENGEL ASTROLABIUM 1494
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*These rare books, printed on presses before 1501, discuss medical knowledge and sciences related to human health. The History of Medicine Division of the National Library of Medicine maintains a collection of more than 500 incunabula (early printed books) and manuscripts that date back to 1094. Medical scholars may use the collection after obtaining special permission. (NIH Photo #1401)*

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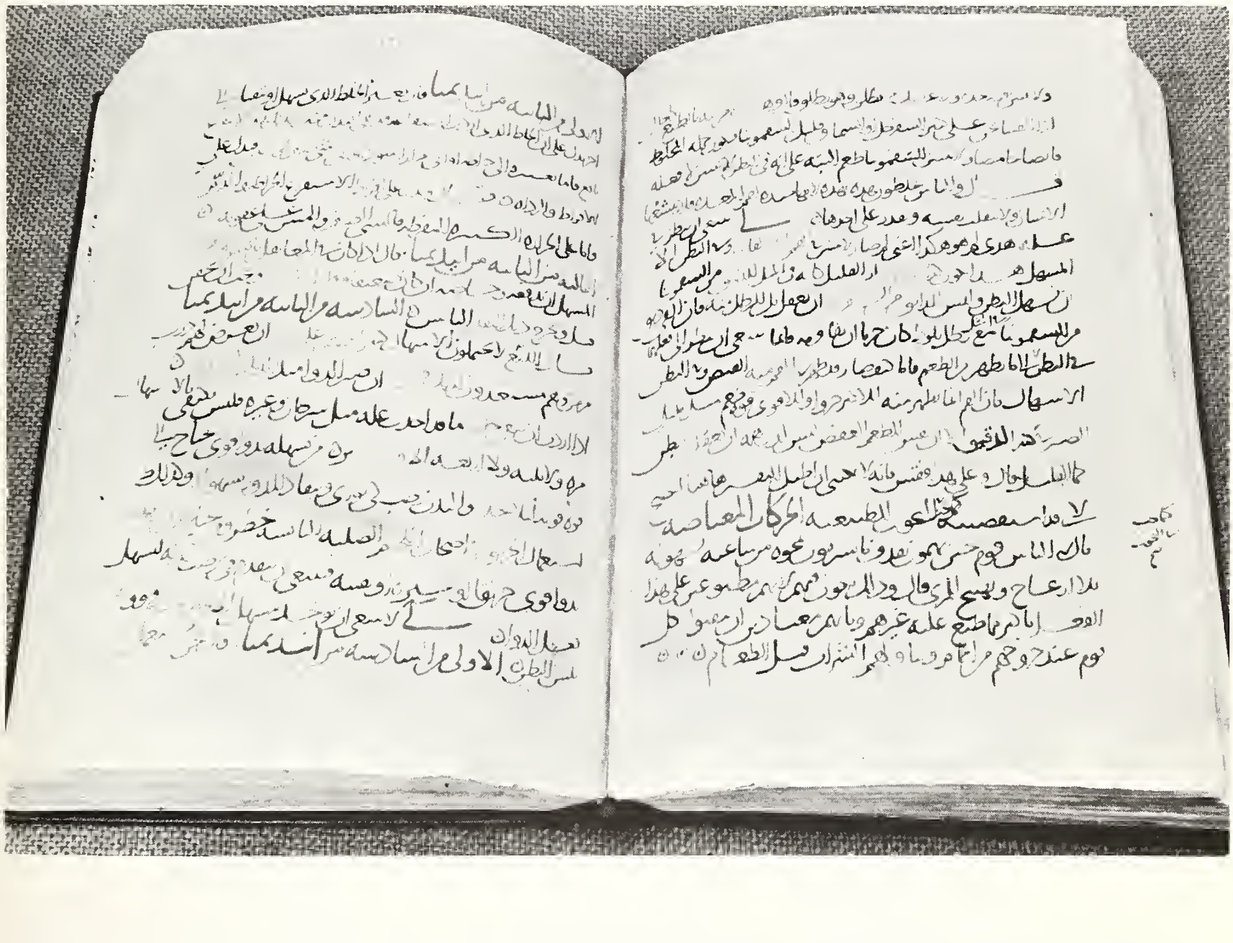

*The earliest work in the collection of the National Library of Medicine is Razes'* **Al-Hawi fi al-tibb** *(The Comprehensive in Medicine). This Arabic volume is Part III, and it deals with gastrointestinal diseases and how to treat them. (NIH Photo #1402)*

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# NATIONAL CANCER INSTITUTE HAS VIRUS ISOLATION FACILITY

*The National Cancer Institute has a research program on the role of viruses in cancer. Vast evidence shows that viruses can cause certain cancers in rodents, chickens, cats, and more recently in sub-human primates. A technician is shown working in one of the protective units in the Institute's Virus Isolation Facility where studies are conducted on feline leukemia viruses.* (NIH Photo #1403)

(more)

Virus Lab (Cont'd)

*A National Cancer Institute scientist is shown mixing media to use in studying viruses. His special interest is investigating leukemia in cats. (NIH Photo # 1404)*

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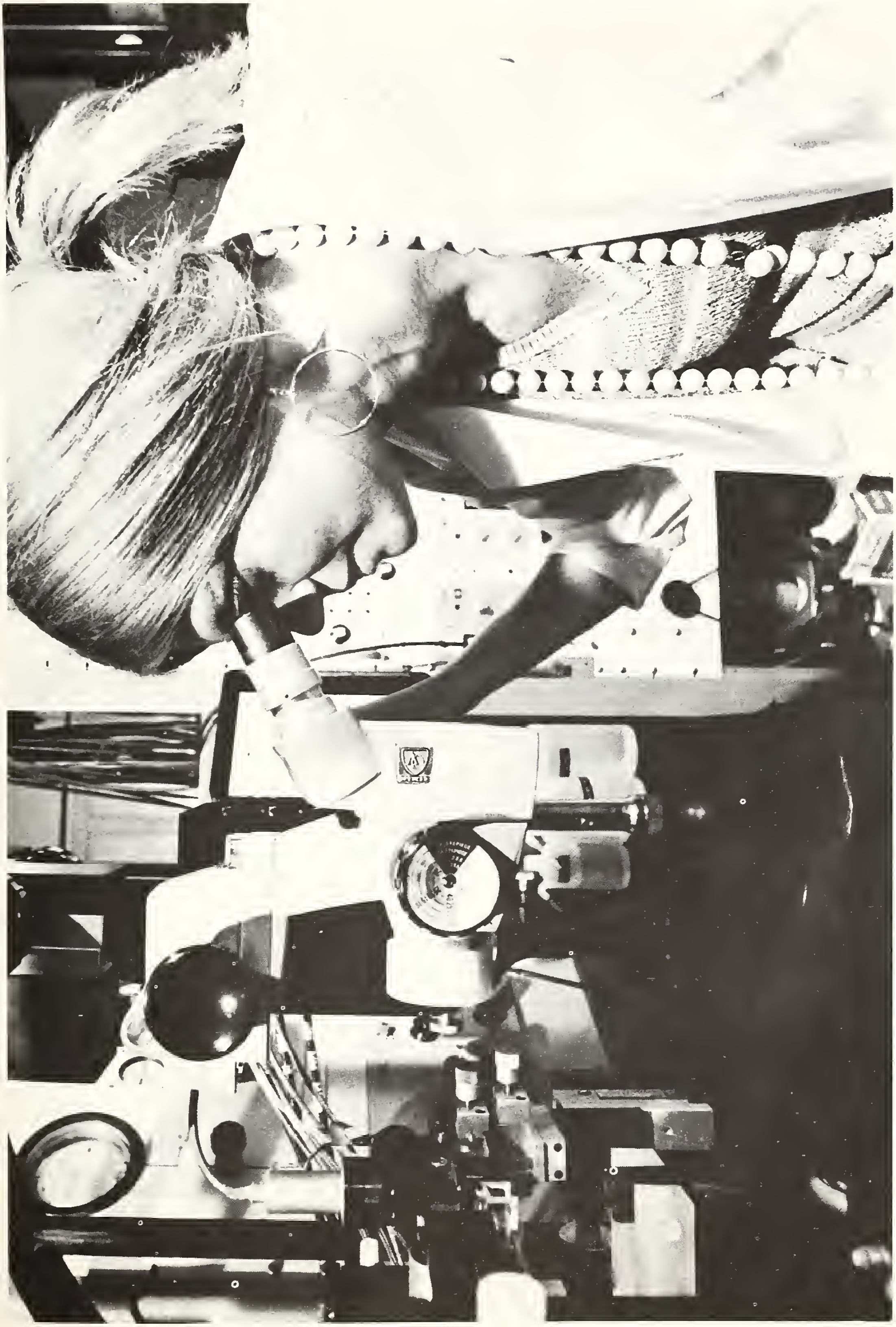
Virus Lab (Cont'd)



*National Cancer Institute investigators use a cytology cell separator to separate and count cancer and normal cells that are being studied.* (NIH Photo # 1405 )

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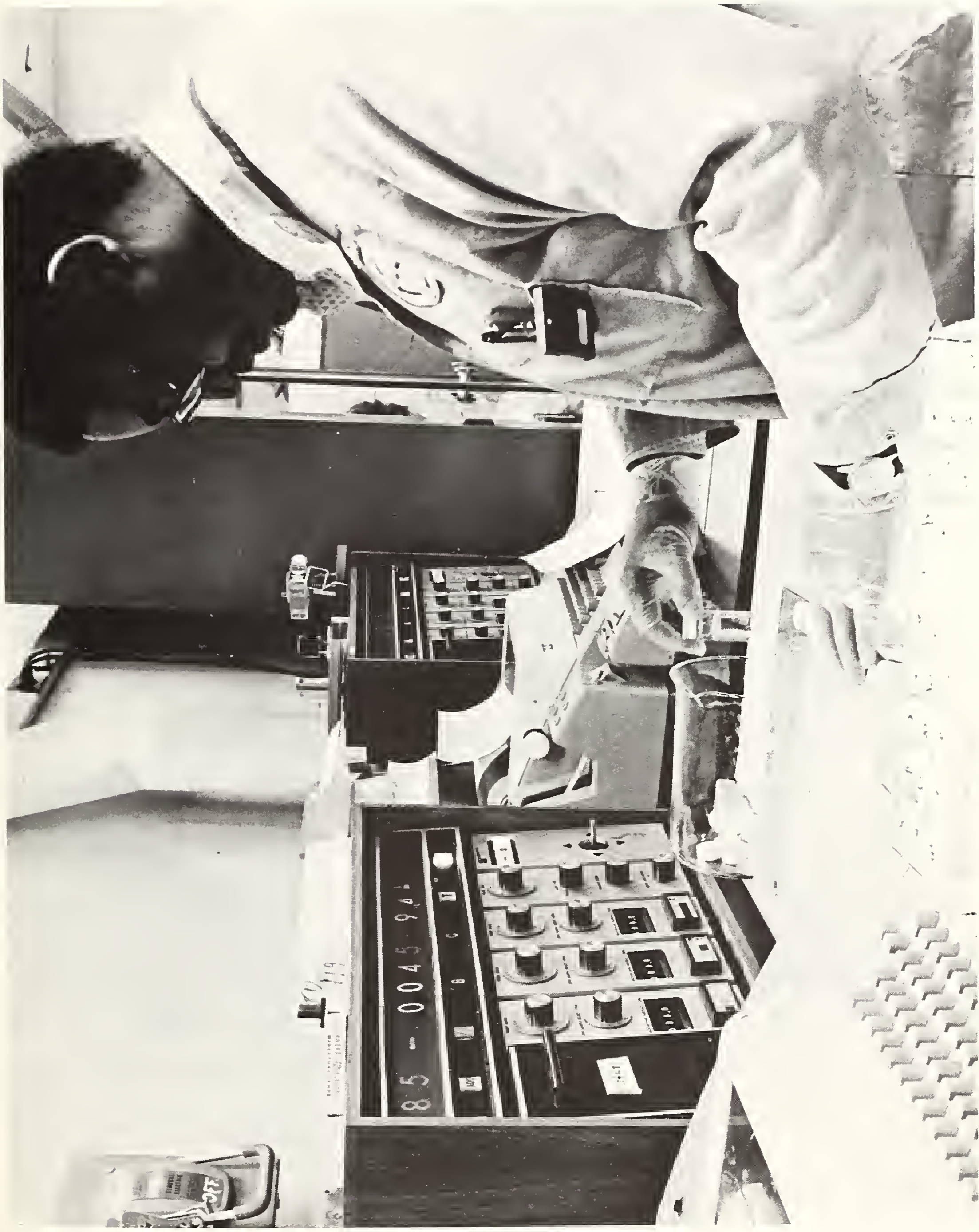
Virus Lab (Cont'd)



*This technician is storing viruses in a special cabinet located in the cancer virus laboratory of the National Cancer Institute.* (*NIH Photo #1406*)

#

Disease Profile

## MOST COMMON INHERITED BLOOD DISORDER IS COOLEY'S ANEMIA

Cooley's anemia is the most common of the thalassemias, a group of genetically determined blood disorders. Also known as Mediterranean anemia or thalassemia major, Cooley's anemia was first described in 1925 by Thomas B. Cooley, M.D., of Detroit.

The main biochemical defect in Cooley's anemia is the body's inability to produce red blood cells with a sufficient amount of hemoglobin, a substance that enables the red cells to carry oxygen. Normal red blood cells have a life span of three to four months, and as they die they are continuously replaced by new cells. In Cooley's anemia the red blood cells cannot survive for more than a few weeks, resulting in anemia that appears shortly after birth and becomes progressively worse as time passes.

Cooley's anemia is inherited as the "double dose" of a hereditary defect. This means that both parents must carry and transmit the trait for Cooley's anemia to their child for the child to develop the disease. Although individuals whose ancestors were natives of the countries surrounding the Mediterranean Sea (particularly Italy and Greece) are most likely to inherit Cooley's anemia, the American "melting pot" has distributed the gene defect through intermarriage to approximately 200,000 Americans of varied backgrounds. One out of every thousand American children of Mediterranean descent will inherit Cooley's anemia.

Individuals who inherit the hereditary defect from only one parent will develop thalassemia minor which can either manifest itself as a mild form

(more)

of anemia or may present no symptoms at all. Since this condition never worsens or converts to thalassemia major, individuals with thalassemia minor have a normal life span and normal health.

The earliest signs of Cooley's anemia, which are similar to those characterizing any type of anemia, are pallor, listlessness, loss of energy and appetite, and irritability. A physician's examination often reveals an enlargement of the spleen and liver, pallor of the skin and mucous membrane, and sometimes a slight yellow coloration, called jaundice, in the whites of the eyes. A blood test will show the changes in the shape and number of red blood cells that distinguish Cooley's from most other anemias.

Children with the disease are usually small for their age because their bone growth is poor, and their bones are sometimes so fragile that fractures occur almost spontaneously. The anemia causes them to tire easily and robs them of energy.

Because there is no simple screening test, diagnosis of thalassemia minor can be accomplished only by performing a number of blood tests that detect changes in the size, shape, fragility, and content of the red cells.

The only way to maintain a blood count sufficient for survival is to administer periodic blood transfusions, for some patients every two to four weeks, and for others at longer intervals. In addition to the transfusions, the victims of Cooley's anemia must undergo surgical removal of their spleens in some cases, and may endure many unpredictable complications of the disease caused by an increased susceptibility to infection.

(more)

The hundreds of pints of transfused blood create a buildup of an excessive amount of iron, which becomes deposited in the patient's body and vital organs, including the heart. Once iron has been deposited in these tissues it cannot be removed by any normal life process, and the only chemical agents that can remove this excess iron are too toxic for widespread clinical use. The resulting iron overload can cause the development of such conditions as cardiac and liver failure, kidney failure, diabetes, and hepatitis, any of which can eventually lead to death.

Studies in the fields of hematology and genetics are essential to provide a better insight into blood mechanisms and the genetic basis of inherited blood disorders such as Cooley's anemia.

The Federal Government is expanding and intensifying its campaign directed against Cooley's anemia. At the National Institute of Arthritis, Metabolism, and Digestive Diseases, scientists are continuing their investigation of the basic mechanisms of this disease. Clinical and laboratory studies are also being conducted by the National Heart and Lung Institute. Meanwhile, it is hoped that better understanding of the disease and improved management of its complications will enable those afflicted with Cooley's anemia to live longer with less pain and disability.

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## News Releases Issued

DES EFFECTS--Scientists at the National Institute of Environmental Health Sciences have developed a method of testing the toxic effects of diethylstilbestrol (DES), a synthetic hormone, on unborn animals.

Recent reports have described the latent appearance of previously rare genital tract tumors in young women whose mothers had been given DES during gestation. During the 1950s and 1960s, a number of women having trouble with their pregnancies were given the drug to keep them from aborting.

Using mice in their experimental model, the investigators will try to determine how and when damage to offspring of DES-treated mothers occurs.

The experiment should also be useful in studying factors associated with transplacental carcinogenesis.

The very early ovaries are being taken from unborn mice and grown in culture. Some are then being traced through the normal process of development and studied to see how changes occur when there is no interference. Other cells of the same kind are being exposed to DES to determine what changes occur in the way the cells develop.

In studies with the DES-exposed mice so far, no visible changes in the development of the whole animal have been found. The offspring appear to grow normally and to reach puberty normally. There is some evidence, however, that reproductive tract lesions may be produced in male offspring following DES exposure during gestation. Work will continue at the Institute to learn whether male offspring of DES-treated mothers may also be at risk.

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(more)

CANCER SURVIVAL--The National Cancer Institute has released a report comparing the survival from cancer among 219,493 white and 21,088 black patients whose disease was diagnosed between 1955 and 1964 in selected American hospitals.

The Institute scientists found that cancers of the digestive tract, reproductive organs, and bladder were diagnosed at a localized stage more often in the white patients than in the black patients.

Black-white differences with respect to extent of disease at diagnosis were less apparent for cancers of the pancreas, lung, kidney, and brain, which are more difficult to detect at an early stage.

"Treatment and Survival Patterns for Black and White Cancer Patients Diagnosed 1955 through 1964" cites generally lower survival rates among black patients as compared to white patients in the study.

Results of the study suggest that whites use modern screening and diagnostic techniques more frequently than blacks. This pattern may be due in part to socioeconomic, cultural, and perhaps other as-yet-unidentified factors.

Survival rates generally were lower among the black patients even when their disease was diagnosed at a localized stage. This difference was greatest among patients with bladder cancer and among females with cancer of the body of the uterus. However, for cancers of the kidney, survival was more favorable among black patients than white patients.

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VISION RESEARCH--A new report by an advisory council to the National Eye Insti-

(more)

tute is expected to have considerable impact on the future course of vision research support in the United States. Intended to focus attention on the most crucial problems and promising opportunities facing vision scientists, the report is the first detailed and comprehensive analysis of public and private support of vision research in the U.S.

The report evaluates the current status of the Institute's five major research programs, and identifies research needs and opportunities in (1) Retinal and Choroidal Diseases, (2) Corneal Diseases, (3) Cataract, (4) Glaucoma, and (5) Sensory and Motor Disorders of Vision. It also evaluates research training support, and endorses research grants to scientists and institutions as the primary way to develop new knowledge in the field.

Recommending systematic priorities to achieve "modest redirection rather than major alterations" in selected programs, the report calls for program planning as an aid to solving major blinding and visual health problems. The report's ultimate aim is to provide structure and guidance for the development of the Nation's vision research effort over the next few years.

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